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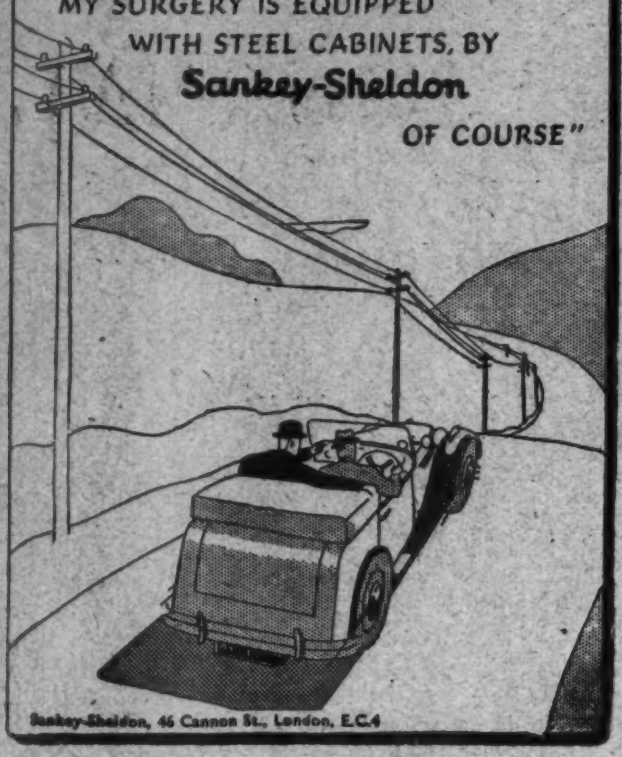

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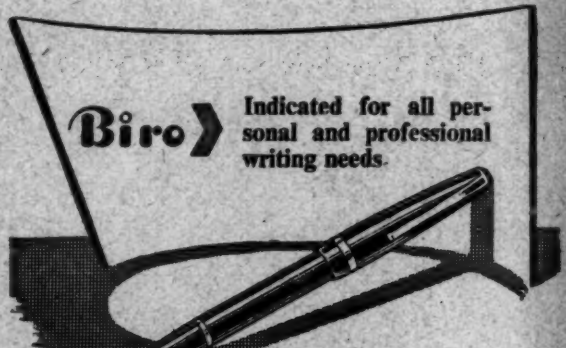

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BRITISH MEDICAL JOURNAL

LONDON SATURDAY OCTOBER 30 1948

STREPTOMYCIN TREATMENT OF PULMONARY TUBERCULOSIS

A MEDICAL RESEARCH COUNCIL INVESTIGATION

The following gives the short-term results of a controlled investigation into the effects of streptomycin on one type of pulmonary tuberculosis. The inquiry was planned and directed by the Streptomycin in Tuberculosis Trials Committee, composed of the following members: Dr. Geoffrey Marshall (chairman), Professor J. W. S. Blacklock, Professor C. Cameron, Professor N. B. Capon, Dr. R. Cruickshank, Professor J. H. Gaddum, Dr. F. R. G. Heaf, Professor A. Bradford Hill, Dr. L. E. Houghton, Dr. J. Clifford Hoyle, Professor H. Raistrick, Dr. J. G. Scadding, Professor W. H. Tytler, Professor G. S. Wilson, and Dr. P. D'Arcy Hart (secretary). The centres at which the work was carried out and the specialists in charge of patients and pathological work were as follows:

Brompton Hospital, London.—Clinician: Dr. J. W. Crofton, Streptomycin Registrar (working under the direction of the honorary staff of Brompton Hospital); Pathologists: Dr. J. W. Clegg, Dr. D. A. Mitchison.

Colindale Hospital (L.C.C.), London.—Clinicians: Dr. J. V. Hurford, Dr. B. J. Douglas Smith, Dr. W. E. Snell; Pathologists (Central Public Health Laboratory): Dr. G. B. Forbes, Dr. H. D. Holt.

Harefield Hospital (M.C.C.), Harefield, Middlesex.—Clinicians: Dr. R. H. Brent, Dr. L. E. Houghton; Pathologist: Dr. E. Nassau.

Bangour Hospital, Bangour, West Lothian.—Clinician: Dr. I. D. Ross; Pathologist: Dr. Isabella Purdie.

Killingbeck Hospital and Sanatorium, Leeds.—Clinicians: Dr. W. Santon Gilmour, Dr. A. M. Reevie; Pathologist: Professor J. W. McLeod.

Northern Hospital (L.C.C.), Winchmore Hill, London.—Clinicians: Dr. F. A. Nash, Dr. R. Shoulman; Pathologists: Dr. J. M. Alston, Dr. A. Mohun.

Sully Hospital, Sully, Glam.—Clinicians: Dr. D. M. E. Thomas, Dr. L. R. West; Pathologist: Professor W. H. Tytler.

The clinicians of the centres met periodically as a working subcommittee under the chairmanship of Dr. Geoffrey Marshall; so also did the pathologists under the chairmanship of Dr. R. Cruickshank. Dr. Marc Daniels, of the Council's scientific staff, was responsible for the clinical co-ordination of the trials, and he also prepared the report for the Committee, with assistance from Dr. D. A. Mitchison on the analysis of laboratory results. For the purpose of final analysis the radiological findings were assessed by a panel composed of Dr. L. G. Blair, Dr. Peter Kerley, and Dr. Geoffrey S. Todd.

Introduction

When a special committee of the Medical Research Council undertook in September, 1946, to plan clinical trials of streptomycin in tuberculosis the main problem faced was that of investigating the effect of the drug in pulmonary tuberculosis. This antibiotic had been discovered two years previously by Waksman (Schatz, Bugie, and Waksman, 1944); in the intervening period its power of inhibiting tubercle bacilli *in vitro*, and the results of treatment in experimental tuberculous infection in guinea-pigs, had been reported; these results were strikingly better than those with any previous chemotherapeutic agent in tuberculosis. Preliminary results of trials in clinical tuberculosis had been published (Hinshaw and Feldman, 1945; Hinshaw, Feldman, and Pfuetze, 1946; Keefer *et al.*, 1946); the clinical results in pulmonary tuberculosis were encouraging but inconclusive.

The natural course of pulmonary tuberculosis is in fact so variable and unpredictable that evidence of improvement or cure following the use of a new drug in a few cases cannot be accepted as proof of the effect of that drug. The history of chemotherapeutic trials in tuberculosis is filled with errors due to empirical evaluation of drugs (Hart, 1946); the exaggerated claims made for gold treatment, persisting over 15 years, provide a spectacular example. It had become obvious that, in future, conclusions regarding the clinical effect of a new chemotherapeutic agent in tuberculosis could be considered valid only if based on adequately controlled clinical trials (Hinshaw and Feldman, 1944). The one controlled trial of gold treatment (and the only report of an adequately controlled trial in tuberculosis we have been able to find in the literature) reported negative therapeutic results (Amberson, McMahon, and Pinner, 1931). In 1946 no controlled trial of streptomycin in pulmonary tuberculosis had been undertaken in the U.S.A. The Committee of the Medical Research Council decided then that a part of the small supply of streptomycin allocated to it for research purposes would be best employed in a rigorously planned investigation with concurrent controls.

The many difficulties of planning and conducting a trial of this nature are important enough to warrant a full description here of the methods of the investigation.

Plan and Conduct of the Trial

Type of Case

A first prerequisite was that all patients in the trial should have a similar type of disease. To avoid having to make allowances for the effect of forms of therapy other than bed-rest, the type of disease was to be one not suitable for other forms of therapy. The estimated chances of spontaneous regression must be small. On the other hand, the type of lesion should be such as to offer some prospect of action by an effective chemotherapeutic agent; for this reason old-standing disease, and disease with thick-walled

cavities, should be excluded. Finally the age group must be reasonably limited, since the total number of patients in the trial could not be large.

Such closely defined features were considered indispensable, for it was realized that no two patients have an identical form of the disease, and it was desired to eliminate as many of the obvious variations as possible. For these several reasons the type of case to be investigated was defined as follows: acute progressive bilateral pulmonary tuberculosis of presumably recent origin, bacteriologically proved, unsuitable for collapse therapy, age group 15 to 25 (later extended to 30).

The selection of this type of disease constituted full justification for having a parallel series of patients treated only by bed-rest, since up to the present this would be considered the only suitable form of treatment for such cases. Additional justification lay in the fact that all the streptomycin available in the country was in any case being used, the rest of the supply being taken up for two rapidly fatal forms of the disease, miliary and meningeal tuberculosis.

Recruitment and Admission of Cases

Co-operation in the trial was obtained in the first place from Brompton Hospital (drawing on London County Council cases), Colindale Hospital (London County Council), and Harefield County Hospital (Middlesex County Council). The L.C.C. and the M.C.C. gave full co-operation, permitting recruitment of suitable cases from the areas served by them, covering a population of nearly six million persons. Accordingly letters were sent, through the tuberculosis departments of these authorities, to tuberculosis officers and to medical superintendents of general hospitals outlining the proposed trial and asking that particulars and *x*-ray films of possibly suitable patients be sent to the co-ordinator of the trials for consideration. Visits were paid to the tuberculosis clinics and hospitals to show by representative *x*-ray films the type of case sought and to explain in detail the nature of the controlled trial. When cases were submitted the clinical particulars and *x*-ray films were taken to the Committee's selection panel for consideration. When a patient had been accepted as suitable, request was made through the local authority for admission to one of the streptomycin centres; in spite of long waiting-lists these patients were given complete priority, and the majority were admitted within a week of approval.

The first patients to be accepted were admitted to the centres in January, 1947. At first the impression was that cases of the type defined are seen often. In fact, such cases are not common. As it became evident after three months that enough cases could not be found in the London and Middlesex areas, other authorities were approached. The Welsh National Memorial Association, the Department of Health for Scotland, and the Leeds Tuberculosis Service made available centres at Sully, Bangour, and Killingbeck, and cases were recruited to those centres from the respective areas. In addition, another centre was opened in the London area, at the Northern Hospital (L.C.C.).

By September, 1947, 109 patients had been accepted, and no more were admitted to this trial. Two patients had died within the preliminary observation week; these are excluded from the analysis. Of the remaining 107 patients 55 had been allocated to the streptomycin group and 52 to the control group.

The Control Scheme

Determination of whether a patient would be treated by streptomycin and bed-rest (S case) or by bed-rest alone (C case) was made by reference to a statistical series based on random sampling numbers drawn up for each sex at each centre by Professor Bradford Hill; the details of the series were unknown to any of the investigators or to the co-ordinator and were contained in a set of sealed envelopes, each bearing on the outside only the name of the hospital and a number. After acceptance of a patient by the panel, and before admission to the streptomycin centre, the appropriate numbered envelope was opened at the central office; the card inside told if the patient was to be an S or a C case, and this information was then given to the medical officer of the centre. Patients were not told before admission that they were to get special treatment. C patients did not know throughout their stay in hospital that they were control patients in a special study; they were in fact treated as they would have been in the past, the sole difference being that they had been admitted to the centre more rapidly than was normal. Usually they were not in the same wards as S patients, but the same regime was maintained

It was important for the success of the trial that the details of the control scheme should remain confidential. It is a matter of great credit to the many doctors concerned that this information was not made public throughout the 15 months of the trial, and the Committee is much indebted to them for their co-operation.

By definition, cases accepted for the trial were unsuitable for collapse therapy; clinicians were therefore asked to adopt collapse therapy only if the course of the disease so changed that some collapse measure became indispensable and urgent. In the S cases collapse therapy was in fact never applied during the four treatment months. It was given to five of the 52 C cases during that period.

Observation and Treatment Period

Each patient was to remain in bed at the centre for at least six months, and the results were to be assessed on the clinical status at the end of that period. In addition to the usual hospital records, clinical observations were entered on standard record forms designed particularly for this trial; these forms provided for details of history, criteria of acceptance, examination on admission, monthly routine re-examinations with assessment of progress since last examination, observation of toxic reactions, temperature and treatment records, and finally a pathological record form. Instructions on required frequency of examinations were given.

Clinicians and pathologists' meetings were held during the trials to discuss the work as it proceeded. The co-ordinator visited centres and was constantly in touch with the clinicians concerned to discuss the progress of the trial and the problems arising. The working subcommittee of pathologists established the technical laboratory procedures, discussed the findings at intervals, and arranged for independent checking of sensitivity tests of tubercle bacilli and streptomycin levels in the blood.

Analysis of Results

The general trend of results during the course of the trial was followed through the monthly reports from the centres. The analysis of results up to six months after the patient's admission is presented here; it is based on information from the standard record forms completed for each patient and on the *x*-ray films which have been made available by the hospitals concerned.

The films have been viewed by two radiologists and a clinician, each reading the films independently and not knowing if the films were of C or S cases. One of the radiologists had been attached to a centre taking part in the trial; the other two specialists had not been connected with the trial in any way. There was fair agreement among the three; at a final session they met to review and discuss

films on which there had been a difference of interpretation, and agreement was reached without difficulty on all films. The results of radiological assessment presented in the main analyses are the agreed results, but the separate reports and their differences are discussed under the heading "Changes in Radiological Picture."

Condition on Admission

Each patient was under observation at a centre for at least one week before streptomycin treatment or observation proper for the trial started. Data in Table I reflect the condition on admission.

TABLE I.—*Condition on Admission*

General Condition	S Group	C Group	Max. Evening Temp. in First Week*	S Group	C Group	Sedimentation Rate	S Group	C Group
Good	8	8	98–98·9° F. (36·7–37·15° C.)	3	4	0–10	0	0
Fair ..	17	20	99–99·9° F. (37·2–37·75° C.)	13	12	11–20	3	2
Poor ..	30	24	100–100·9° F. (37·8–38·25° C.)	15	17	21–50	16	20
			101° F. (38·3° C.) +	24	19	51 +	36	29
Total	55	52	Total	55	52	Total	55	51†

* Temperature by mouth in all but six cases. †Examination not done in one case.

Thirty patients (54%) in the S group and 24 (46%) in the C group were in poor general condition at the start of the trial; of these, 20 and 17 respectively were considered to be desperately ill. Twenty-four S patients (44%) and 19 C patients (36%) had during the preliminary observation week maximum evening temperatures of 101° F. (38.3° C.) or over. In 36 S patients (65%) and 29 C patients (56%) the sedimentation rate (Westergren, 200 mm. reading at one hour) was over 50.

These data reflect the fairly acute clinical condition of most of the patients, though obviously the clinical picture was far from uniform in the 107 patients admitted to the trial. The data show also that random distribution has equalized the groups; if anything, there are more severe cases in the S group. There were 22 men and 33 women in the S group, 21 men and 31 women in the C group.

X-ray Classification

All cases conformed more or less to the type defined, but within the possible limits of the definition there were wide variations. All films showed opacities representing extensive infiltration of apparently recent origin; where there was room for doubt the length of history was taken into consideration as evidence of the age of the lesions.

It was thought at first that gross cavitation should be excluded, but this view was abandoned, as many otherwise suitable cases had large cavities. Thirty-two of the 55 S cases and 30 of the 52 C cases showed large or multiple cavities in the film taken on admission (tomography was not used as a routine); it must be stressed, however, that from their radiological appearance these seemed to be of recent development and that the lesions predominating in the lungs were bronchopneumonic in type.

In 19 S cases and in 19 C cases there was radiological evidence of segmental atelectasis.

Treatment

All S patients were given streptomycin* by the intramuscular route. The dose was 2 g. per day, given in four injections at six-hourly intervals. This dosage was adopted following exchange of correspondence with Dr. H. C. Hinshaw, of the Mayo Clinic, to whom the Committee is indebted for advice during the planning of the trial.

The original intention was to continue streptomycin treatment for six months. However, reports from observers in the U.S.A., and a growing impression in our own centres, indicated that the maximum effect of streptomycin was reached within the first three or four months, and it was therefore decided in July, 1947, to treat patients for four months only, but to continue observation to the end of six months from admission as for C patients. (One patient was treated with streptomycin for 6 months, 2 for 5½ months, 6 for 5 months, 5 for 4½ months; the remainder, 41 patients, were treated for 4 months.)

Patients in both groups were on bed-rest during the period of the trial, and were allowed only up to toilet where the general condition allowed. As already indicated, although patients admitted were considered unsuitable for collapse therapy, it was agreed that when the course of disease had so changed that collapse therapy was strongly indicated such treatment should be given. In 11 C patients collapse measures (artificial pneumoperitoneum with phrenic paralysis in 10 cases, pneumothorax in one) were induced at some time during the six months—three in the third month of observation, two in the fourth month, two in the fifth, and four in the last observation month. In seven of the 11 the course of the disease appears not to have been affected; in four there was deterioration before and improvement after induction of artificial pneumoperitoneum. Collapse therapy was induced in 11 S patients during the fifth or sixth month; in all but two the course of the disease was apparently unaltered.

Results at End of Six Months

Four of the 55 S patients (7%) and 14 of the 52 C patients (27%) died before the end of six months. The difference between the two series is statistically significant; the probability of it occurring by chance is less than one in a hundred.

Assessment of condition at the end of the six-months period should be based on a judicious combination of changes in the radiological picture, changes in general condition, temperature, weight, sedimentation rate, and bacillary content of the sputum. We have not attempted a numerical evaluation of the relative importance of each of these, and changes in them will be reported in turn. Appreciation of the clinical effects of the drug have not been lacking in the many reports published within the past two years. So far as possible, the analysis in this report will deal with the more readily measurable data only.

The following preliminary analysis is based on changes in the radiological picture alone, this being in our opinion the most important single factor to consider; it will be seen later that in the great majority of cases clinical and radiological changes followed similar trends.

TABLE II.—*Assessment of Radiological Appearance at Six Months as Compared with Appearance on Admission*

Radiological Assessment	Streptomycin Group		Control Group	
Considerable improvement ..	28	*51%*	4	*8%*
Moderate or slight improvement	10	*18%*	13	*25%*
No material change	2	*4%*	3	*6%*
Moderate or slight deterioration	5	*9%*	12	*23%*
Considerable deterioration ..	6	*11%*	6	*11%*
Deaths	4	*7%*	14	*27%*
Total	55	*100%*	52	*100%*

The overall results given in Table II (extracted from Table IX) show differences between the two series that leave no room for doubt. The most outstanding difference

*The streptomycin used was in the form of the hydrochloride, obtained from one American producer. For technical particulars of the product see article in *Lancet*, 1948, **1**, 582.

is in the numbers who showed "considerable improvement" in the radiological picture—i.e., those for whom at the end of the six-months period there was a reasonable prospect of recovery. Twenty-eight of the S patients (51%) and only four of the C patients (8%) were considerably improved (the probability of such a difference occurring by chance is less than one in a million).

Results in men and women were similar, and need not be tabulated here. There was a higher mortality among males in both S and C groups; two of 22 male S patients died and eight of 21 male C patients, compared with two of 33 female S patients and six of 31 female C patients, but the difference is not significant.

Results Related to Condition on Admission

The next point to be considered is whether the prognosis was worse in those most acutely ill, and whether the difference between the S and C groups applies to the less or more acutely ill patients.

Temperature

TABLE III.—*Results at Six Months Related to Temperature on Admission*

Max. Evening Temp. during First Observation Week		Radiological Assessment at 6 Months: Improvement	No Change	Deterioration	Deaths	Total
98–98·9° F. (36·7–37·15° C.)	S	3	0	0	0	3
	C	3	1	0	0	4
99–99·9° F. (37·2–37·75° C.)	S	9	1	3	0	13
	C	7	2	2	1	12
100–100·9° F. (37·8–38·25° C.)	S	13	0	2	0	15
	C	5	0	7	5	17
101° F. (38·3° C.)+	S	13	1	6	4	24
	C	2	0	9	8	19

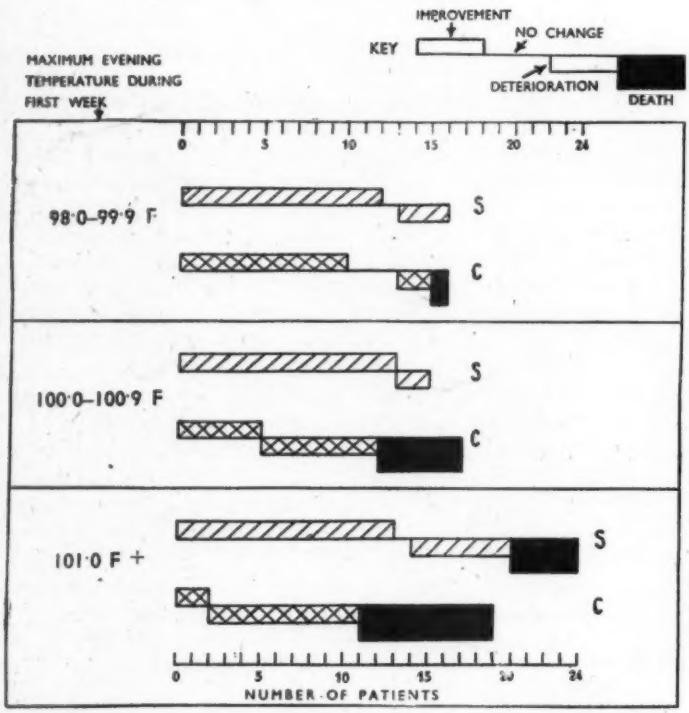

CHART I.—Results at six months (radiological assessment) related to temperature on admission.

The results in Table III, represented graphically in Chart I, show first what was to be expected—viz., in both groups the most grave prognosis was in the patients most febrile on admission; indeed, in the S group the only deaths were in patients who had on admission evening temperatures of 101° F. (38.3° C.) or over. A second, more important, point that emerges is that the superiority of results in the S group as a whole over the C group is almost entirely accounted for by the most febrile patients. Only seven (19%) of 36 C patients with a temperature of 100° F. (37.8° C.) or over were improved at the end of six months, compared with 26 (67%) of 39 S patients. Further analysis reveals that eight of the 24 S patients with a temperature of 101° or over showed considerable improvement, and none of the 19 C patients. In less febrile and in afebrile patients there is little difference in results between the two groups, though analysis shows that the number showing considerable improvement was greater in the S group.

Sedimentation Rate (E.S.R.)

Relation of results to the E.S.R. on admission shows the same trends. Of patients with an E.S.R. not higher than 50, 13 (68%) of 19 S patients were improved, compared with nine (41%) of 22 C patients. Eighteen (50%) of 36 S patients with E.S.R. over 50 were improved, compared with seven (24%) of 29 C patients.

Radiological Assessment on Admission

TABLE IV.—*Radiological Assessment at Six Months Related to Presence or Absence of Gross Cavitation on Admission*

X-Ray on Admission	Group	Total Cases	Radiological Assessment at 6 Months: Improvement: Considerable	Improvement: Slight or Moderate	No Change	Deterioration: Slight or Moderate	Deterioration: Considerable	Deaths
Cases with large or multiple cavities	S	32	11	7	2	4	4	4
	C	30	1	8	2	6	2	11
Other cases	S	23	17	3	0	1	2	0
	C	22	3	5	1	6	4	3

The data in Table IV show that in both S and C groups the results were better where there was no gross cavitation on admission. In the S cases with no gross cavitation the results were outstandingly good, with no deaths and 17 of 23 patients showing considerable improvement.

Clinical Changes During Period of Trial

General Condition

Assessment of changes in general condition is based on a combination of clinical facts, clinician's general impression, and patient's feeling of well- or ill-being. As such, it is mentioned only briefly here. At four months after admission the general condition had improved in 40 (73%) of the 55 S patients, compared with 26 (50%) of 52 C patients; only seven (13%) S patients were worse, whereas 10 (19%) C patients had died and another 13 (25%) were worse than on admission. At six months after admission the difference between the two groups was less; in 33 (60%) S patients and in 24 (46%) C patients the general condition was better than on admission: 13 S patients (24%) were worse and four others (7%) had died; 12 C patients (23%) were worse and 14 others (27%) had died.

Temperature

Three S patients and four C patients were afebrile on admission to the trial. The three S patients remained afebrile throughout, with the exception of a short slight pyrexial episode in one case. Two of the four C patients remained afebrile throughout; the other two had occasional low pyrexia, and one was still pyrexial at the end of the six

MEDICAL RESEARCH COUNCIL: STREPTOMYCIN TREATMENT OF PULMONARY TUBERCULOSIS
CASES DEMONSTRATING "CONSIDERABLE IMPROVEMENT"

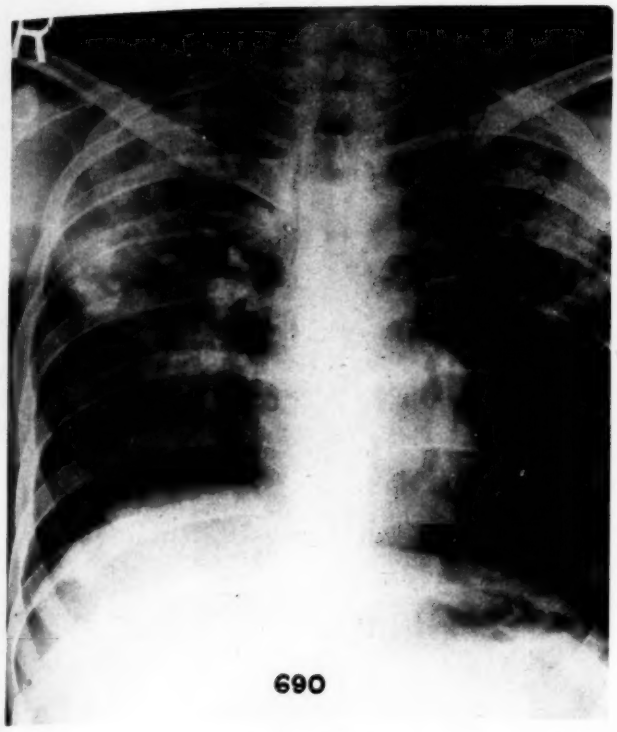

FIG. 1.—Case 69 (S). May 12, 1947.

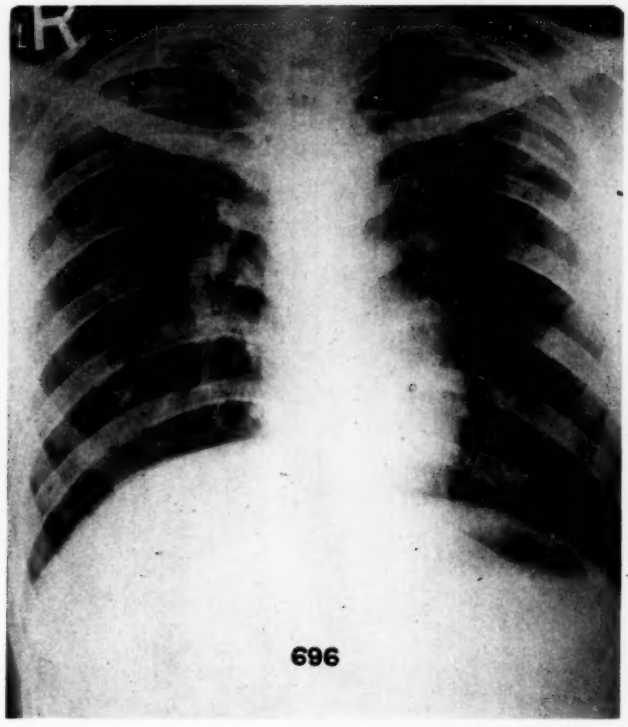

FIG. 2.—Case 69 (S). Nov. 17, 1947.

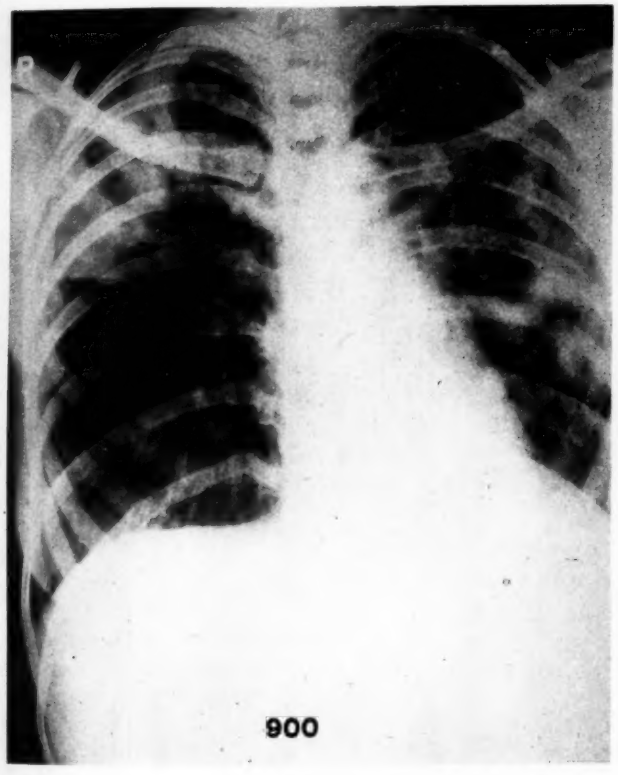

FIG. 3.—Case 90 (S). April 26, 1947.

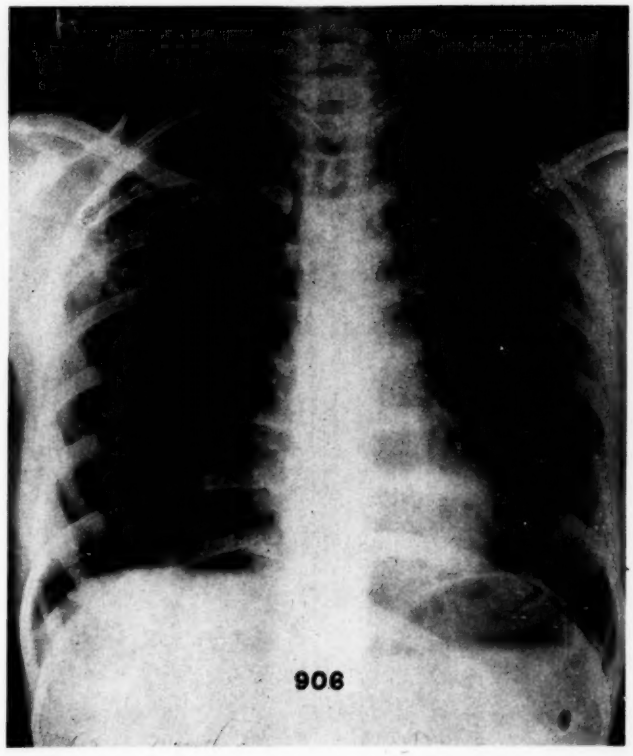

FIG. 4.—Case 90 (S). Nov. 5, 1947.

MEDICAL RESEARCH COUNCIL: STREPTOMYCIN TREATMENT OF PULMONARY TUBERCULOSIS

CASES DEMONSTRATING "CONSIDERABLE IMPROVEMENT"

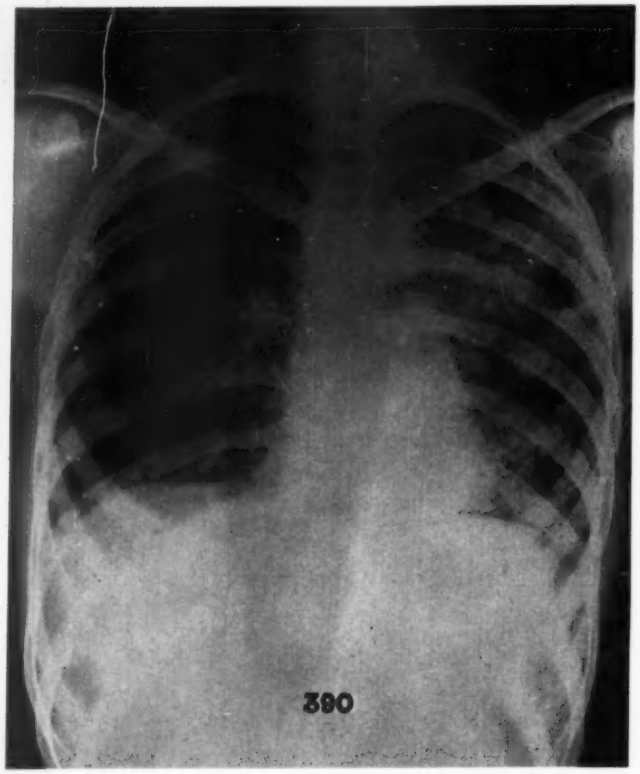

FIG. 5.—Case 39 (S). June 21, 1947.

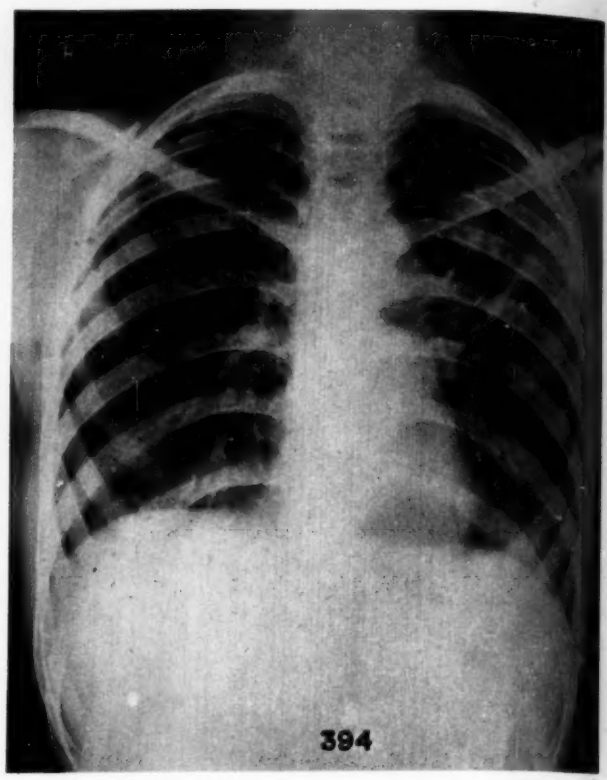

FIG. 6.—Case 39 (S). Oct. 20, 1947.

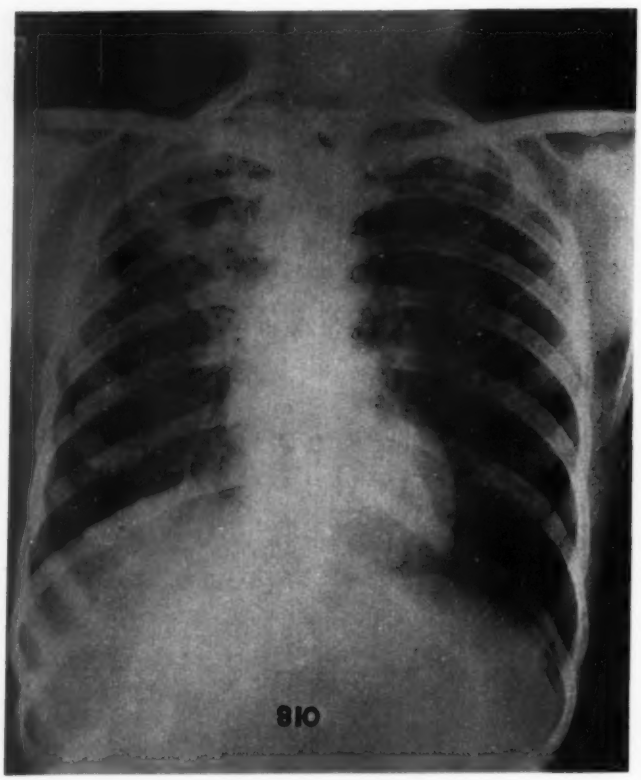

FIG. 7.—Case 81 (C). Feb. 27, 1947.

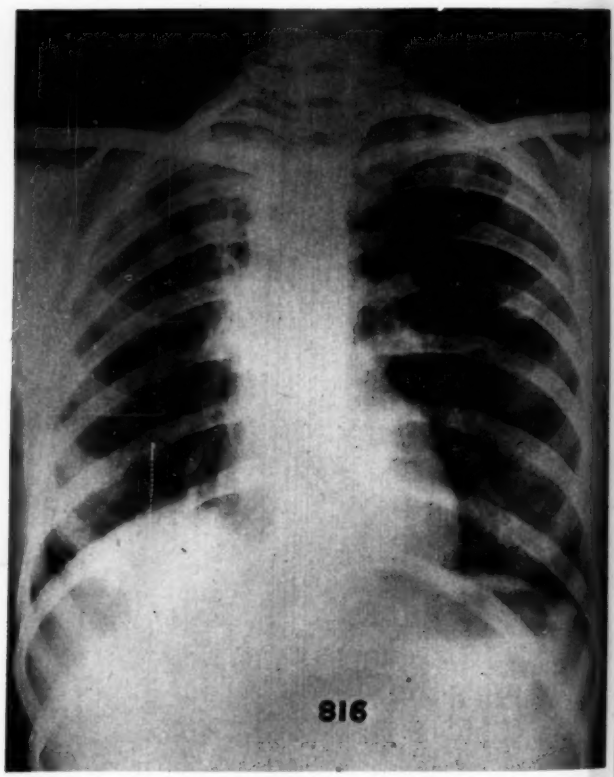

FIG. 8.—Case 81 (C). Aug. 27, 1947.

MEDICAL RESEARCH COUNCIL: STREPTOMYCIN TREATMENT OF PULMONARY TUBERCULOSIS
CASES DEMONSTRATING "MODERATE IMPROVEMENT"

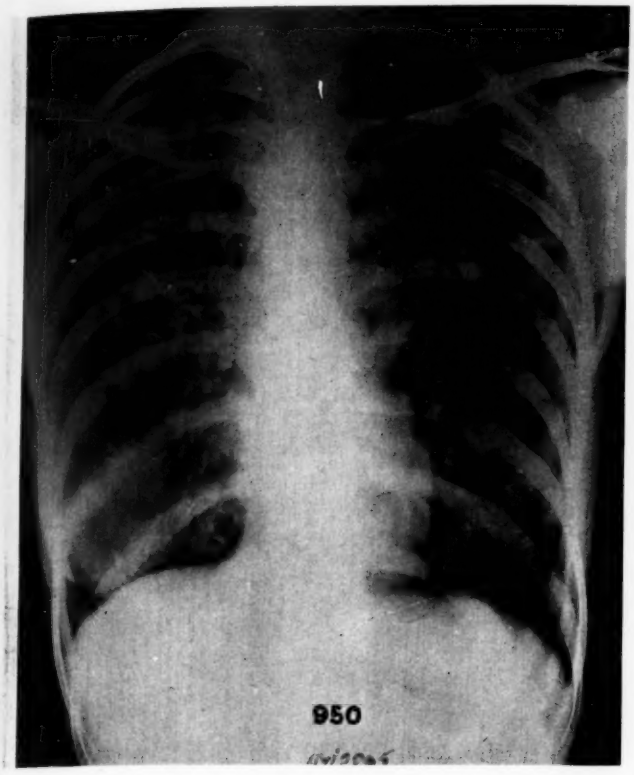

FIG. 9.—Case 95 (S). May 21, 1947.

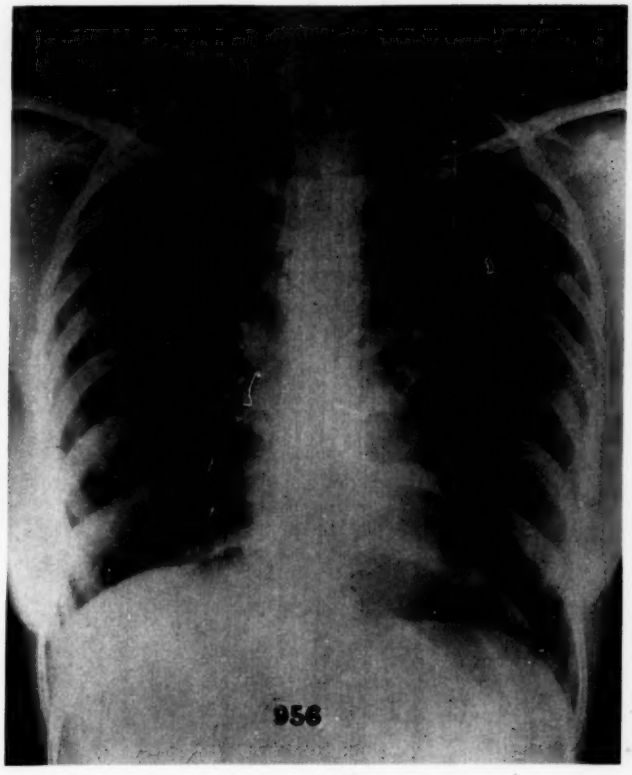

FIG. 10.—Case 95 (S). Nov. 21, 1947.

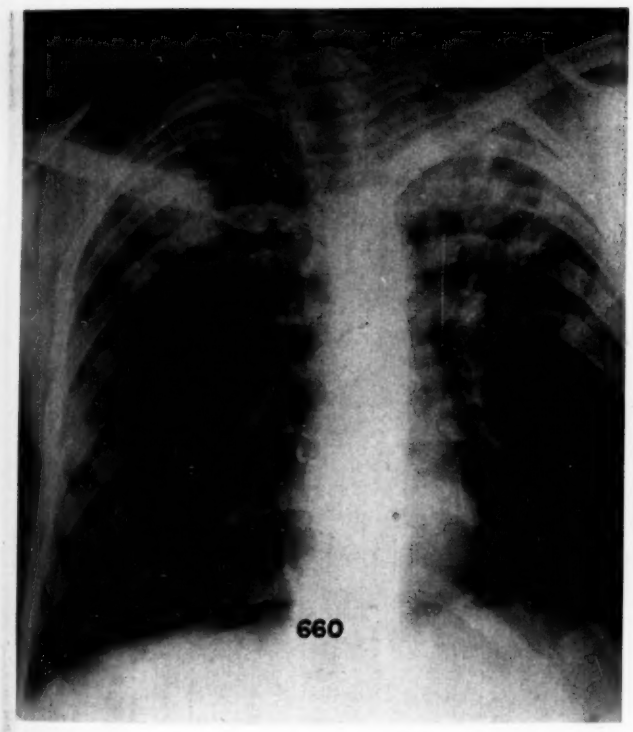

FIG. 11.—Case 66 (C). April 11, 1947.

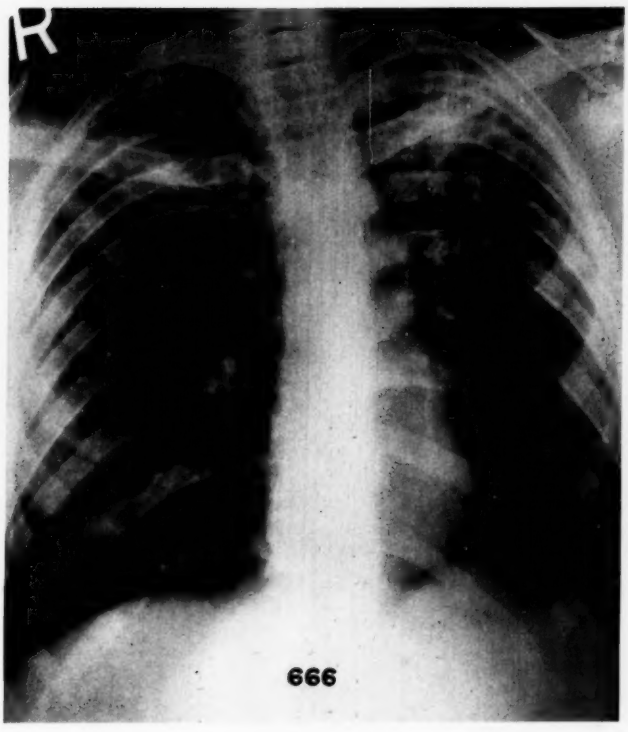

FIG. 12.—Case 66 (C). Oct. 15, 1947.

MEDICAL RESEARCH COUNCIL: STREPTOMYCIN TREATMENT OF PULMONARY TUBERCULOSIS

S CASES: IMPROVEMENT AND SUBSEQUENT DETERIORATION

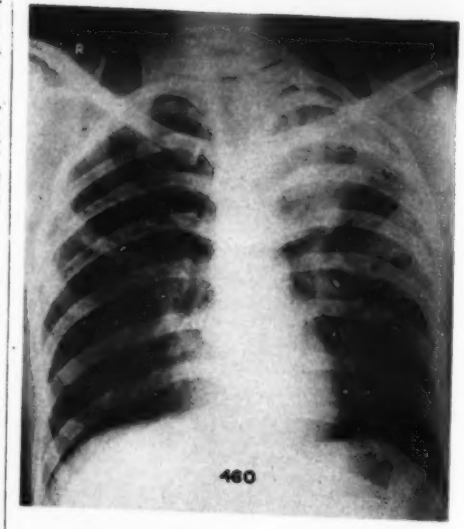

FIG. 13.—Case 40. Jan. 30, 1947.

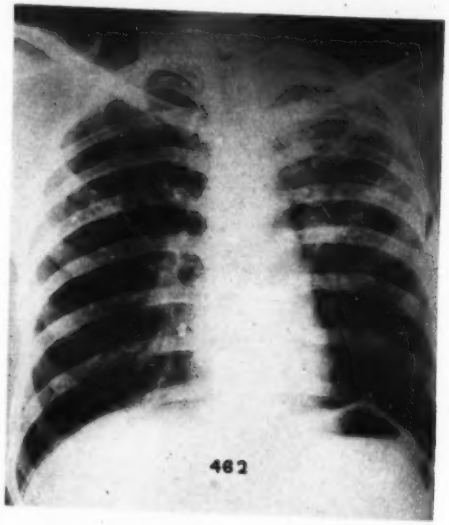

FIG. 14.—Case 46. March 26, 1947.

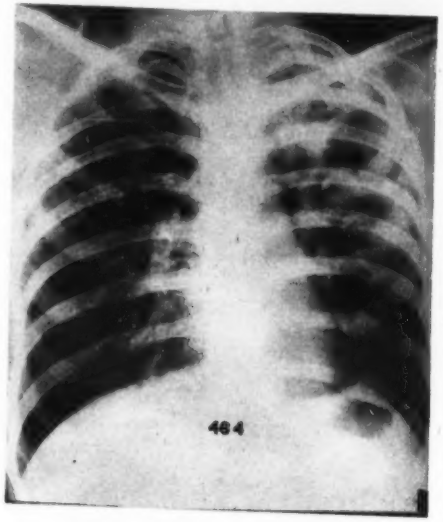

FIG. 15.—Case 46. May 23, 1947.

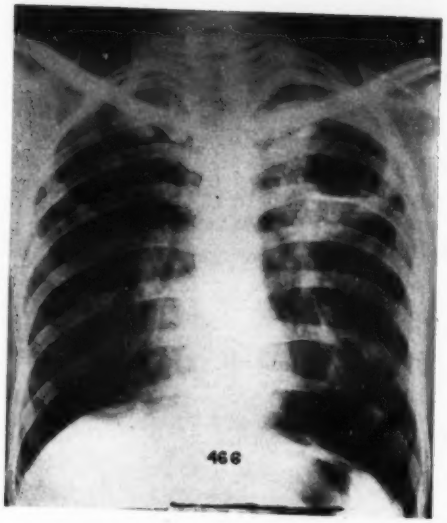

FIG. 16.—Case 46. July 21, 1947.

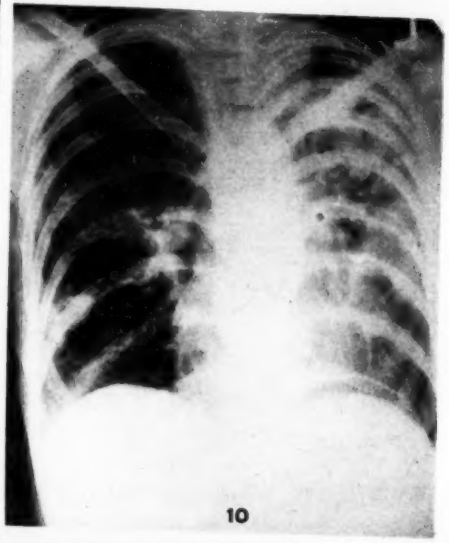

FIG. 17.—Case 1. June 2, 1947.

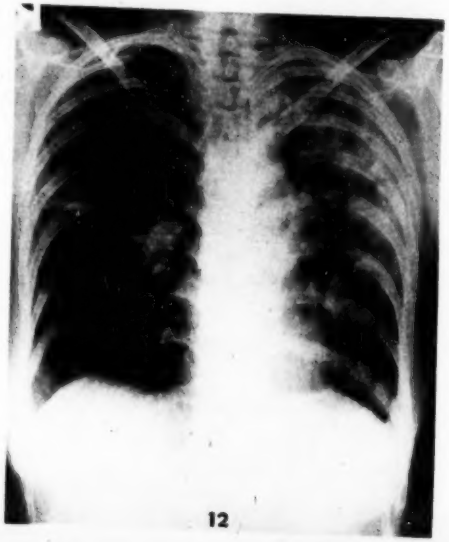

FIG. 18.—Case 1. July 25, 1947.

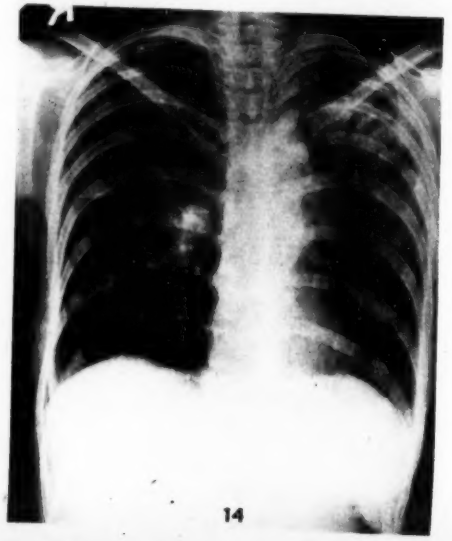

FIG. 19.—Case 1. Sept. 29, 1947.

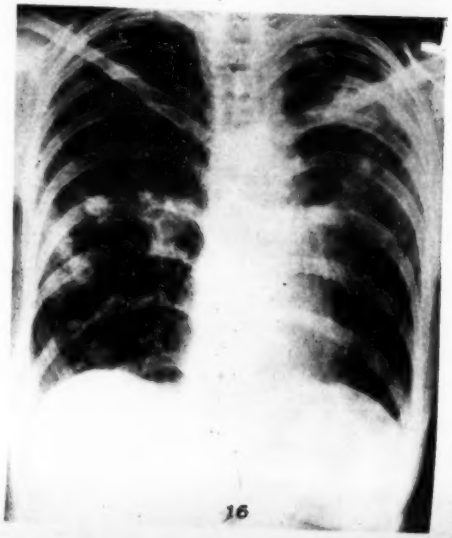

FIG. 20.—Case 1. Nov. 21, 1947.

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months. Temperature changes in the febrile patients at two months, four months, and six months after admission are shown in Table V.

TABLE V.—*Temperature Changes in Patients Febrile on Admission*

Highest Evening Temp. During Week following Admission	Group	Total	No. of Patients whose Temperature was Normal at end of			No. of Patients Showing Temp. Fall (including Fall to Normal) at end of		
			2 Mos.	4 Mos.	6 Mos.	2 Mos.	4 Mos.	6 Mos.
101° F. (38·3° C.) or over	S	24	1	5	6	15	14	11
	C	19	0	2	3	7	6	8
99–100·9° F. (37·2–38·25° C.)	S	28	8	15	18	12	19	24
	C*	28	5	10	10	10	11	12

* Temperature for one C case not available.

The difference between S and C series at any one point of time is not statistically significant, but appears at every stage—i.e., at every stage more S patients than C patients show a temperature drop to normal or to a degree of pyrexia lower than that on admission. A common effect of streptomycin not obvious in the above simplified presentation of data is a rapid temperature drop in the first weeks of therapy, followed sometimes by a rise to a level usually lower than the level on admission. Among the less acutely febrile patients (temperature 99–100.9° F.; 37.2–38.85° C.) an increasing number of S cases show falling temperature; at six months 18 of the 28 were apyrexial and six others had temperatures lower than on admission; 10 of 28 similar C cases were apyrexial and two others had temperatures lower than on admission.

There is thus a consistent difference between S and C groups. It is important to note, however, that in 20 of 47 febrile patients treated by bed-rest without streptomycin the temperature was lower at the end of six months than on admission; in 13 of the 20 it was within normal limits. For the type of lesions selected, these results serve to emphasize both the value of prolonged bed-rest and the need of controls in an investigation of this type.

In seven of the 13 C patients with normal temperature at the end of six months an artificial pneumoperitoneum had been induced at some time during the trial, but in every case the temperature had come down to normal previous to the induction of artificial pneumoperitoneum. The temperature fall in the C patients can be attributed to the effect of bed-rest alone.

Weight (Table VI)

In the first four months 20 S patients had gained weight (5 lb.—2.27 kg.—or more), with a total weight gain between them of 253 lb. (114.76 kg.), mean 12.6 lb. (5.71 kg.). The weight gains in the C group are very similar: 20 patients gained weight, with a total gain of 255 lb. (115.67 kg.), mean 12.7 lb. (5.76 kg.). At the end of six months 24 S patients had gained weight, with a total gain of 451 lb. (204.57 kg.), mean 18.8 lb. (8.53 kg.). Eighteen C patients had gained weight, with a total gain of 313 lb. (141.97 kg.), mean 17.4 lb. (7.89 kg.).

TABLE VI.—*Weight Changes*

Weight Changes	4 Months After Admission		6 Months After Admission	
	S	C	S	C
14 lb. (6·35 kg.) or more gain	8	6	19	12
5–13 lb. (2·27–5·89 kg.) gain	12	14	5	6
Less than 5 lb. (2·27 kg.) gain or loss ..	15	9	12	10
5 lb. (2·27 kg.) or more loss	13	7	11	5
Deaths	0	10	4	14
Total*	48	46	51	47

* Information not available for all cases; some patients too ill to be weighed.

These facts reveal, first, that many patients with a severe form of tuberculosis gained weight on treatment by bed-rest alone; indeed, 12 at the end of six months had gained a stone (6.35 kg.) or more in weight. Secondly, the weight gains in the S group in the first four months were no greater than in the C group, and therefore do not reflect the important improvement observed in other respects; on the other hand, there was more weight gain in the last two months—i.e., after treatment had stopped. It is certain that some patients failed to gain weight, or gained little weight, during the course of streptomycin treatment, and this may be at least partly ascribed to the gastric disturbances, which were severe in a few cases and in others were mild but sufficient to reduce appetite and retard weight gain.

Menstruation

In 10 of 32 female S patients and in 12 of 31 female C patients menstruation was normal on admission and remained normal. In nine S patients and 12 C patients amenorrhoea persisted throughout. In 11 S patients and seven C patients menstruation appeared at some time during observation and remained normal subsequently; in addition two S patients had a temporary return of menstruation.

Sedimentation Rate

TABLE VII.—*Sedimentation Rate*

E.S.R.	Group	On Admission	At 2 Months	At 4 Months	At 6 Months
0–10	S	0	0	6	17
	C	0	1	2	4
11–50	S	19	31	23	17
	C	22	10	15	18
51+	S	36	24	26	15
	C	29	37	23	14
Deaths	S	—	0	0	4
	C	—	2	10	14
Total*	S	55	55	55	53
	C	51	50	50	50

* Totals do not correspond in all columns, as results were not available in all cases.

The data in Table VII show two main differences between groups S and C. If one takes into account the patients who died, in the C group the number of patients with a very high sedimentation rate (over 50) was never reduced; in the S group the number fell from 36 to 19 (including four deaths). Secondly, at six months in only four C patients had the E.S.R. fallen to within normal limits; in the S group the corresponding number was 17.

Changes in Radiological Picture During Period of Trial

After the close of the trial the chest radiographs of all patients were viewed, and changes assessed, by the three members of the radiological panel working separately. They were not told whether films were of patients from S or C series. Radiographs of each patient had been taken on admission and at monthly intervals subsequently. It was decided to make as simple an assessment as possible, reviewing progress at two-monthly intervals, each two-monthly film being compared with the film taken two months previously and with the initial film. Thus the comparisons on which report was requested were: 0 with 2 (initial film with film two months after admission), 2 with 4, 0 with 4, 4 with 6, and 0 with 6. Assessments were required to fall under one of the five headings "considerable improvement," "moderate or slight improvement," "no change," "moderate or slight deterioration," "considerable deterioration." A report "no change" might signify no appreciable change in the radiological picture or improvement in one part of the lung offset by deterioration in another.

FIG. 17.—Case 1. June 2, 1947. FIG. 18.—Case 1. July 25, 1947. FIG. 19.—Case 1. Sept. 29, 1947. FIG. 20.—Case 1. Nov. 21, 1947.

So simple a classification invited difficulties, and these were soon evident. How should atelectasis be classified? Some films showed considerable clearing of infiltration concurrently with enlargement of cavities—radiologically they were both better and worse. The analysis in Table VIII shows the separate results of readings by the three assessors. Two most important readings have been chosen for this analysis: 0 with 4 (comparison of initial film with film four months after admission) and 4 with 6.

TABLE VIII.—*Comparison of Radiological Assessments by Three Assessors*

Interval	Group	Total Cases	Assessor	Radiological Assessment				
				Improvement		No Change	Deterioration	
				Considerable	Slight or Mod.		Slight or Mod.	Considerable
Admission to end of 4th month	S	55	X	18	24	4	5	4
			Y	27	17	3	4	4
			Z	27	15	1	6	6
	C	42	X	0	11	4	18	9
			Y	2	10	11	10	9
			Z	3	8	8	15	8
End of 4th month to end of 6th month	S	51	X	2	17	11	15	6
			Y	5	18	10	8	10
			Z	3	12	11	19	6
	C	38	X	0	11	18	7	2
			Y	2	9	19	5	3
			Z	1	10	11	14	2

It can be seen from Table VIII that there was some disagreement among the three members of the panel, but the outstanding differences between results in S and C groups remain unaffected.

Where reports were identical they were adopted as the final agreed report. Where the reports on a case by the three members fell in two adjoining columns of the classification (e.g., "considerable improvement" and "slight or moderate improvement") the majority of two was taken as the final agreed report. In all other cases there was held to be disagreement. Thus in the comparisons between radiograph on admission and radiograph at four months there was agreement in 76 cases and disagreement in 21. In the comparisons between radiographs at four months and at six months there was agreement in 75 cases and disagreement in 14.

At a final session the three members of the radiological panel met for discussion and review of films on which there had been disagreement. After a short discussion it was agreed that changes in the prognosis for the patient should be taken as the base-line of assessment. In a comparison of two radiographs of a patient the question should be, judging from these films alone, Has the outlook for the patient become better or worse? On this basis the films in question were reviewed, and agreement was reached on all of them. The analysis which follows is based on the agreed results. The overall results under the five different headings are given for each of the three assessments 0:2, 0:4, and 0:6 in Table IX and Chart II, and for each of the three assessments 0:2, 2:4, 4:6 in Table X and Charts III and IV.

It is evident that at every stage there is between the two groups a great difference in the course of the disease.

At two months 76% of S patients showed radiological improvement, and in 14% the improvement was considerable; only 6% of C patients were improved, and in none was the improvement considerable. Of C patients 4% had died and another 38% were worse than on admission; 11% of S patients were worse, and none had died.

From the end of the second month to the end of the fourth month the proportion of S patients who improved (65%) was slightly lower than in the first two months and the corresponding proportion of C patients (18%) was higher, but the difference between the two groups is still marked. Considering the overall change in the first four months, 78% of S patients were improved and only 21% of C patients; in none of the latter and in 45% of S patients the improvement was considerable. Of C patients 19% had died and another 42% were worse than on admission; no S patients had died and only 14% had deteriorated.

The proportion of S patients who improved in the fifth and sixth months was again lower than before (34% compared with 65% in the third and fourth months and 76% in the first two months); this can be seen clearly in Chart III and IV. Of S patients 7% died in that period and another 31% deteriorated (the total 38% compares with 20% in the preceding two months and 11% in the first two

TABLE IX.—*Changes in the Radiological Picture*

Interval	Group	Total	Radiological Assessment								Deaths	
			Improvement				No Change		Deterioration			
			Considerable		Slight or Mod.				Slight or Mod.	Considerable		
Admission to end of 2nd month	S	55 100%	8	14%	34	62%	7	13%	5 9%	1 2%	0	
	C	52 100%	0		3	6%	27	52%	14 27%	6 11%	2	6%
Admission to end of 4th month	S	55 99%	25	45%	18	33%	4	7%	4 7%	4 7%	0	
	C	52 99%	0		11	21%	9	17%	14 27%	8 15%	10	19%
Admission to end of 6th month	S	55 100%	28	51%	10	18%	2	4%	5 9%	6 11%	4	7%
	C	52 100%	4	8%	13	25%	3	6%	12 23%	6 11%	14	27%

TABLE X.—*Changes in the Radiological Picture*

Interval	Group	Total	Radiological Assessment								Deaths	
			Improvement				No Change		Deterioration			
			Considerable		Slight or Mod.				Slight or Mod.	Considerable		
Admission to end of 2nd month	S	55 100%	8	14%	34	62%	7	13%	5 9%	1 2%	0	
	C	52 100%	0		3	6%	27	52%	14 27%	6 11%	2	6%
End of 2nd month to end of 4th month	S	55 100%	6	11%	30	54%	8	15%	8 15%	3 5%	0	
	C	50 100%	0		9	18%	13	26%	16 32%	4 8%	8	16%
End of 4th month to end of 6th month	S	55 99%	3	5%	16	29%	15	27%	10 18%	7 13%	4	7%
	C	42 100%	1	2%	9	21%	17	41%	9 21%	2 5%	4	10%

months); 10% of C patients surviving at four months died and another 26% deteriorated. Despite the setback in S patients in later months, the result at six months compared with the condition on admission shows, as we saw in the preliminary analysis, a remarkable difference between the two groups.

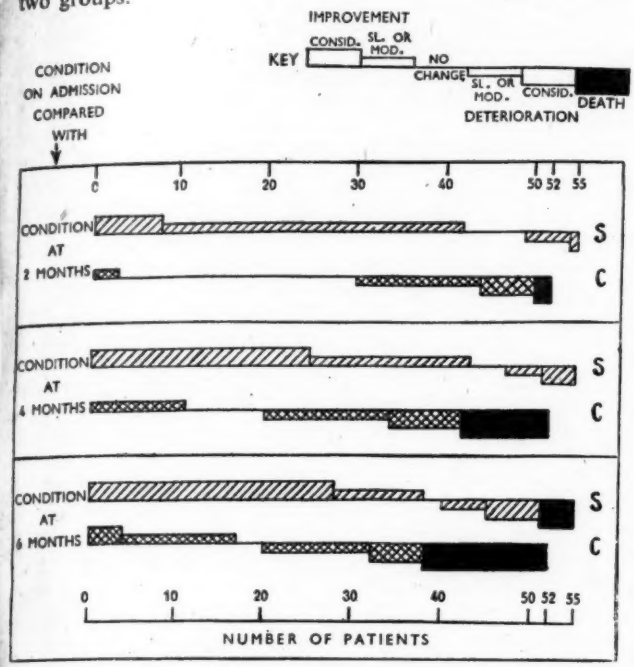

CHART II.—Condition on admission compared with condition at two, four, and six months (radiological assessment).

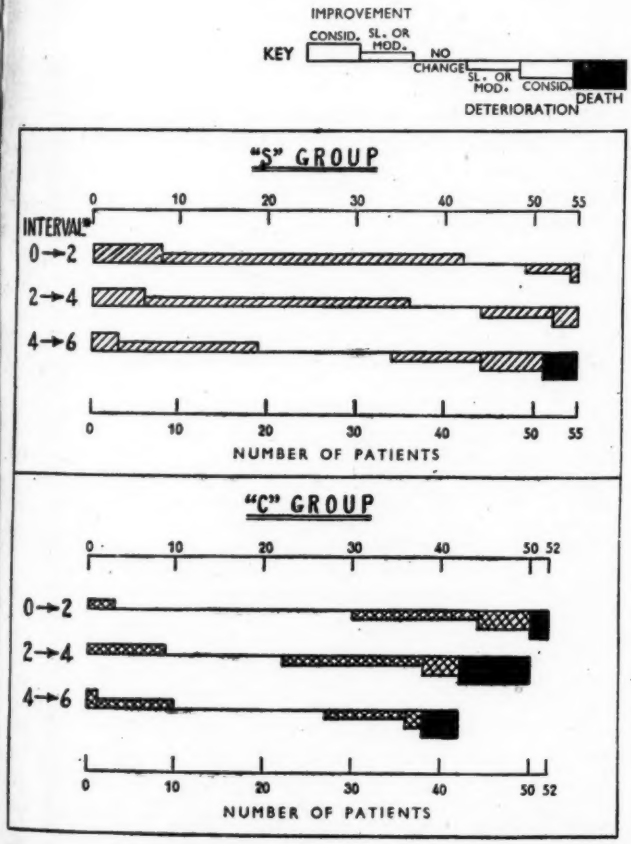

CHART III.—Changes in the radiological picture in succeeding two-monthly periods. 0→2, admission to end of second month; 2→4, end of second month to end of fourth month; 4→6, end of fourth month to end of sixth month.

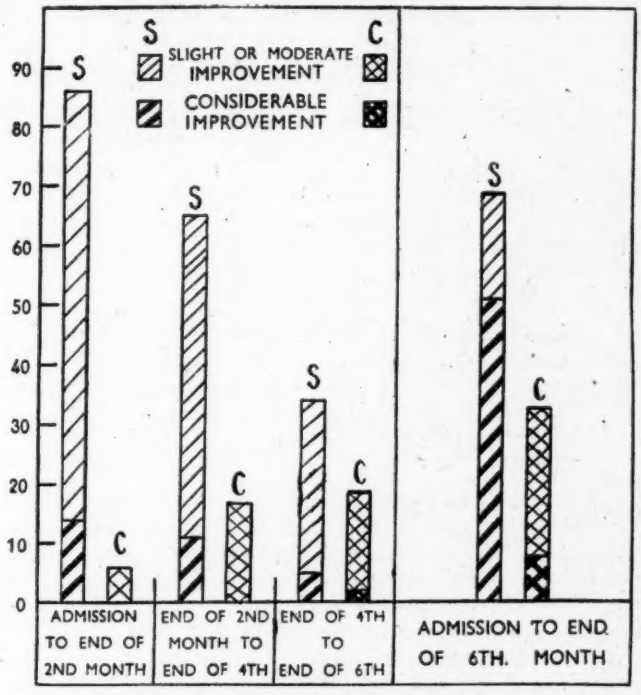
SLIGHT OR MODERATE IMPROVEMENT
CONSIDERABLE IMPROVEMENT
S
C
0 10 20 30 40 50 60 70 80 90
ADMISSION TO END OF 2ND MONTH
END OF 2ND MONTH TO END OF 4TH
END OF 4TH TO END OF 6TH
ADMISSION TO END OF 6TH. MONTH

CHART IV.—Percentage of total patients admitted (*not* of survivors at beginning of each period) showing improvement in radiological picture in succeeding two-monthly periods and in six months.

It is of interest to analyse in greater detail the changes that occurred from period to period. The analysis in Tables XI and XII relates results in succeeding two-monthly periods.

TABLE XI.—*Radiological Changes in Succeeding Periods (S Cases)*

Admission to End of 2nd Month	Total	End of 2nd Month to End of 4th Month			
		Improvement	No Change	Deterioration	Deaths
Improvement ..	42	31	6	5	0
No change ..	7	4	1	2	0
Deterioration ..	6	1	1	4	0
Total ..	55	36	8	11	0
End of 2nd Month to end of 4th Month	**Total**	**End of 4th Month to End of 6th Month**			
Improvement ..	36	17	12	7*	0
No change ..	8	1	1	5†	1
Deterioration ..	11	1	2	5	3
Total ..	55	19	15	17	4

* One case had begun to deteriorate in the fourth month, though the overall assessment 2 : 4 was improvement.

† Two cases had begun to deteriorate in the fourth month, though the overall assessment 2 : 4 was no change.

Thirty-one of 42 S patients who improved in the first two months continued to improve in the third and fourth months, but less than half of those who improved in the third and fourth months made further good progress subsequently. Nearly all S patients who deteriorated in the first months continued to get worse subsequently; only one of the six in the first two months and one of the 11 in the third and fourth months improved subsequently; the improvement in the latter case began only after induction of pneumoperitoneum.

Considering now the 17 S patients who deteriorated and four who died in the fifth and sixth months, eight had been getting worse during the preceding two months, six more had shown "no change," and seven had improved in the preceding two months. These cases are analysed in detail later.

Analysis of radiological changes in the C group (Table XII) shows that here patients who improved did so much more slowly. Only three patients improved in the first two

Table XII.—*Radiological Changes in Succeeding Periods (C Cases)*

Admission to End of 2nd Month	Total	End of 2nd Month to End of 4th Month			
		Improvement	No Change	Deterioration	Deaths
Improvement ..	3	0	2	1	0
No change ..	27	9	9	8	1
Deterioration ..	20	0	2	11	7
Total ..	50	9	13	20	8
End of 2nd Month to end of 4th Month	**Total**	**End of 4th Month to End of 6th Month**			
Improvement ..	9	2	7	0	0
No change ..	13	5	4	4	0
Deterioration ..	20	3	6	7	4
Total ..	42	10	17	11	4

months, and they did not continue to improve subsequently. Nine patients showed improvement in the third and fourth months. In all nine the condition had been stationary in the first two months; the improvement was attributable to bed-rest alone—only one of these patients had collapse therapy, three and a half months after admission. None of the nine deteriorated in the fifth and sixth months, contrary to what was seen in the S group. On the other hand, as in the S group, nearly all patients who deteriorated in the first two months continued to deteriorate subsequently—i.e., for those who showed no response to the first two months of bed-rest and streptomycin, or bed-rest alone, the outlook was poor.

Six of the 10 C patients who improved in the fifth and sixth months received collapse therapy; in four of them the improvement was considered due to these measures.

Clinical Observations on Cases Showing Improvement

In the preceding sections various clinical and radiological changes have been analysed separately, the analysis showing for each factor differences between S and C groups. Below are additional data and some representative case histories to give a more complete picture of patients' progress under treatment.

Considerable Improvement in S Cases

Of the 28 S patients who radiologically had improved considerably at the end of six months 11 had been regarded as desperately ill on admission. All 28 improved from the first month of treatment. In none could the improvement even in later months be ascribed to collapse therapy.

(*a*) Twenty-one of the 28 improved clinically in all respects—i.e., their general condition and symptoms improved, they gained weight, temperature and E.S.R. fell, 18 were apyrexial at the end of six months, and 16 had gained more than 14 lb. (6.35 kg.) in weight. In eight cases the sputum had become negative to all examinations for tubercle bacilli.

Case 69.—A man aged 25 had been ill for four months and had been in hospital since shortly after the clinical onset. Artificial pneumothorax had been attempted, but failed; on complete bed-rest throughout the four months he continued to deteriorate. On admission to the centre he was exceedingly ill, wasted, with laryngitis, with swinging temperature 99.4–103.4° F. (37.4–39.7° C.), sedimentation rate 66, sputum heavily positive. The chest radiograph showed confluent opacities of broncho-pneumonic type throughout both upper and mid-zones, and scattered foci in the lower zones (Plate, Fig. 1). During the first two months there was slight clinical improvement: fever persisted, though at a lower level; the sedimentation rate was unchanged; the sputum was negative on direct examination and positive on culture. The chest radiograph showed little change. During the next months there was a striking turn for the better: symptoms regressed, the laryngitis improved; from the end of the fourth month he was apyrexial; he gained 42 lb. (19.05 kg.) weight from the third to the sixth month (on admission he had been too ill to weigh). The sedimentation rate had fallen to 22. Sputum was still positive, though on culture only. Radiologically there was remarkable clearing of lesions (Fig. 2).

Case 90.—A woman aged 24 had been ill for two months; her condition had been aggravated by recent parturition and post-partum haemorrhage. She was in hospital for two weeks before admission to the streptomycin centre. She was desperately ill on admission, wasted, and had a pyrexia varying from 99 to 103.4° F. (37.2–39.7° C.); sedimentation rate 150. On the chest radiograph were dense confluent opacities throughout the left lung, with some cavitation, and less extensive lesions in the right lung (Fig. 3). She remained critically ill during the first week of treatment, after which there was marked improvement in her general condition and symptoms. The evening temperature fell to 100° F. (37.8° C.) at the end of the second month, and from the end of the fourth month she was apyrexial. Weight gain was only 4 lb. (1.8 kg.). The sedimentation rate fell progressively to 20 at the end of six months. The sputum and material from gastric lavage were negative to all methods of examination for tubercle bacilli from the 59th day onwards. There was considerable radiological clearing of lesions (Fig. 4). "The result on discharge must be regarded as dramatic" (report by clinical registrar).

(*b*) Seven of the 28 patients improved clinically in most respects, but six were still pyrexial at six months, and the other, though apyrexial, remained in poor general condition, with no weight gain and a high E.S.R. (Case 39, Figs. 5 and 6).

Considerable Improvement in C Cases

Considerable improvement in the radiological picture was reported for only four C patients. None were acutely ill on admission. In none of them had the sputum become negative at the end of six months.

In Case 73 there was general clinical improvement, beginning in the first month, but the marked radiological improvement dated only from the induction of artificial pneumoperitoneum three and a half months after admission. In Case 80 also there was improvement in all respects, but only after induction of pneumoperitoneum two and a half months after admission.

In the two others, Cases 81 and 96, the improvement was attributable to bed-rest alone. Both improved clinically but retained a low pyrexia.

Case 81.—A woman aged 22 had a six-months history of illness, and had been in bed at home for six weeks. On admission she looked ill and wasted, and had a low pyrexia (97.4–99° F. (36.3–37.2° C.)) and a sedimentation rate of 110. Chest radiography showed scattered nodular shadows throughout both lungs, denser at the apices, with a large cavity in the right upper zone (Fig. 7). From the first weeks her general condition improved, and in the six months she gained 28 lb. (12.7 kg.). She retained, however, a low evening pyrexia, the sedimentation rate at the end of six months was 85, and the sputum was positive on culture. Radiologically there was considerable regression and shrinkage of lesions, and the cavity system in the right upper zone was less obvious (Fig. 8).

Slight or Moderate Improvement in S Cases

At the end of six months, of 10 S patients who showed radiologically slight or moderate improvement five were apyrexial, four had sedimentation rates not above 10, and two had gained over 14 lb. (6.35 kg.) in weight. In none of the 10 cases was the sputum negative, though in two it had been negative at some time during treatment and became positive again later.

Case 95.—A woman aged 25 was extremely ill when admitted. She had a history of symptoms for about five

months, and had been in bed at home for four weeks. On admission she had a temperature swinging between 99 and 102.4° F. (37.2 and 39.1° C.), and was very weak and wasted. The sedimentation rate was 28, the sputum heavily positive. There was extensive infiltration in the lungs, particularly in the right lung, where there were large cavities; a calcified primary complex was clearly definable on that side (Fig. 9). Clinically she made excellent progress throughout the six months, with remarkable improvement in the first two months of treatment, and she gained 28 lb. The evening temperature had fallen to 99° F. (37.2° C.) at the end of two months, and shortly after became normal and remained normal. The sedimentation rate fell to 5. The sputum was negative at four months, but subsequently was occasionally positive. Radiologically there was little change in the first two months and improvement subsequently, with clearing at the right base and cavities much less obvious at the right apex (Fig. 10).

Slight or Moderate Improvement in C Cases

Of 13 C patients who showed slight or moderate improvement radiologically at the end of six months, eight had improved clinically in all respects; three of the eight had been clinically very ill on admission. In two the sputum became negative (in one of the two after artificial pneumoperitoneum). Ten were apyrexial at six months, and six had gained over 14 lb. In most of these cases the clinical improvement was much greater than that seen in the lung radiographs.

Case 66.—A man aged 23, ill for about six weeks, had been admitted to a general hospital as a case of appendicitis one month before his admission to the centre. His general condition was fairly good, symptoms were slight, the temperature ranged from 97.6 to 100.2° F. (36.4 to 37.9° C.), the sedimentation rate was 70. There was shadowing throughout the upper and mid-zones of both lungs, particularly dense and with cavitation on the left side (Fig. 11). During the six months of observation there was slow but progressive overall improvement; he put on 24 lb. (10.88 kg.) in weight, symptoms improved, he was afebrile after the third month, three consecutive sputum specimens at the end of the fifth and sixth months were negative. Radiologically there was moderate improvement, with some shrinkage of lesions particularly on the right (Fig. 12).

Deterioration in S Cases

(*a*) In six patients there was radiological deterioration in the first two months. In two of these (Cases 87 and 99) there was no clinical response to treatment, and they continued to deteriorate until death in the fifth or sixth month. Two others (Cases 22 and 40) continued to deteriorate radiologically; clinically there was temporary improvement in the general condition, but temperature and E.S.R. remained high; one (Case 22) died in the fifth month. One (Case 16) continued to deteriorate radiologically (deterioration confined to one lung), but the temperature fell to normal limits, the patient gained weight, and felt much better until after treatment stopped; E.S.R. remained high, over 70. The sixth of these patients improved subsequently in the opinion of the radiologists' panel, but deteriorated clinically. Four of the six had gross cavitation on admission.

(*b*) In seven patients other than those just mentioned there was radiological deterioration through the third and fourth months. Five (Cases 46, 49, 60, 64, and 86) had improved radiologically in the first two months, and there had been temporary clinical improvement; in Case 60 there was marked clinical improvement until a spontaneous pneumothorax occurred three months after admission.

Case 46.—A man aged 25 had been ill for six weeks with cough, dyspnoea, lassitude, loss of weight. He had been resting in bed at home for five weeks before admission to the streptomycin centre. On admission his condition was fair, his temperature ranged from 97.6 to 102° F. (36.4 to 38.9° C.), the sedimentation rate was 40. Chest radiograph showed extensive scattered lesions in upper and mid-zones of both lungs and a large cavity in the left mid-zone. There was slight clinical improvement in the first two months of treatment, symptoms regressed, the temperature fell to a range of 97.8–99.4° F. (36.55–37.4° C.); the sedimentation rate was unchanged and weight was stationary. The clinical change was not of the same order as the change in the radiological picture, which showed considerable improvement (see Figs. 13 and 14). During the third month the clinical condition was stationary except that the temperature began to rise again, and radiologically there was extension and more cavitation of the lesions in the left lung. He then began to lose weight (7 lb.—3.18 kg.—in the fourth month), to feel tired again, and radiographs showed further deterioration with extensive cavitation; a spontaneous pneumothorax occurred in the sixth month (Figs. 15 and 16). The sputum had remained positive throughout; on the 65th day of treatment and subsequently strains of tubercle bacilli from the sputum were 8,000 times less sensitive to streptomycin than the strains isolated before treatment.

In the other two of the seven patients (Cases 54 and 105) the pulmonary condition was stationary radiologically in the first two months; one (Case 105) deteriorated clinically throughout the first months and until after induction of artificial pneumoperitoneum in the fifth month, after which there was radiological improvement also; the other was slightly better clinically in the first months of treatment, but the radiological worsening was rapidly followed by clinical deterioration, and she continued to go downhill. All seven of these cases which deteriorated radiologically for the first time in the third and fourth months had gross cavitation on admission, and five also had some atelectasis.

(*c*) Three other patients (Cases 11, 26, and 59) on whom the radiological report for the second two-month period was "no change" or "improvement" had begun to deteriorate radiologically in the fourth month—i.e., before treatment stopped. In Case 26 spontaneous pneumothorax was diagnosed in the fifth month. In Cases 26 and 59 clinical deterioration also began in the fourth month; in Case 11 only in the sixth month, after a haemoptysis. All three continued to get worse in the last months. Case 59 was the only one of these to have gross cavitation on admission.

(*d*) In nine cases radiological deterioration did not occur until the last two months. In three of these (Cases 28, 77, and 101) the radiological report for the third and fourth months was "no change"; two of them had improved in the first two months, but at the end of the fourth month all three were still febrile and had a high E.S.R. In Case 28 the temperature fell to normal in the first two months and the patient gained 11 lb. (4.98 kg.) in weight, but the temperature rose in the third month, and there was subsequently continued clinical deterioration.

Finally, radiological deterioration in the fifth and sixth months was seen in six patients who had improved radiologically to the end of the fourth month. In two of these (Cases 7 and 24) there had been little or no clinical response to streptomycin treatment; at four months they were pyrexial, had lost over a stone in weight, and had a high E.S.R.; both had gross cavitation on admission. The others (Cases 1, 4, 29, and 71) had improved clinically to the end of the fourth month, though at that date three were still pyrexial and none had an E.S.R. below 40. Only one of these four had gross cavitation on admission.

Case 1.—A woman, aged 24, had been ill for about 10 weeks, and for six weeks before admission had been in bed at home. She was very ill when admitted, pale, wasted, with severe dyspnoea and lassitude; the temperature ranged from 100 to 104.2° F. (37.8 to 40.1° C.), the sedimentation rate was 98, the sputum was strongly positive. The chest radiograph showed

extensive shadowing of bronchopneumonic type throughout both lung fields, more dense in the left lung than in the right (Fig. 17). In the first month the temperature dropped to a range of 99–101° F. (37.2–38.3° C.), and remained at this level during the rest of the four months of treatment. In the first month also there was definite improvement both in symptoms and in general appearance, and she gained 7 lb. (3.18 kg.) in weight. At the end of two months the sputum was negative to direct examination and culture, and radiologically there was some clearing of the lesions, especially on the right. In the third and fourth months she began to lose her feeling of well-being, appetite deteriorated, and she lost 5 lb. (2.27 kg.) in weight; sputum became again heavily positive (strains were 250 times less sensitive to streptomycin than strains isolated before treatment). Radiographs, however, showed further considerable clearing of lesions (Figs. 18 and 19). After treatment was stopped she felt better for a short time, but in the sixth month the condition deteriorated, symptoms were worse, the temperature rose to the same level as on admission, and radiographs at the end of the sixth month showed increased cavitation in the left lung and fresh lesions in the right (Fig. 20).

This analysis has shown that though 21 S patients deteriorated radiologically in the fifth and sixth months—i.e., at a time when no streptomycin was being given in most cases—there is much evidence of commencing deterioration or arrested improvement before the end of the fourth month. Only six of the 21 had been improving radiologically throughout the preceding two months; two of the six had lost weight, and five had remained pyrexial since admission. Moreover, it is noteworthy that in patients who received streptomycin for more than four months results were similar to those for patients treated for four months only; deterioration in the fifth and sixth months was seen in five of 13 patients treated for more than four months, compared with 16 of 42 patients treated for four months only. However, in one patient treated for five months deterioration started in the sixth month. While there is suggestive evidence in a few cases that deterioration was related to cessation of treatment, it is very probable that some factor other than this is responsible in the majority of cases that deteriorated.

Gross cavitation may be a factor in determining relapse after first improvement. Of 16 patients who deteriorated at some time after first improvement, 11 (69%) had large or multiple cavities on admission; of 30 patients who improved throughout, 14 (47%) had large or multiple cavities. The difference is not statistically significant.

Spontaneous pneumothorax occurred in four S patients. In Case 60 it occurred at three months; the patient had been much improved until then, but subsequently went downhill rapidly and died. In two other cases deterioration had begun before the pneumothorax occurred. At first the impression was that this was a particular risk in the S group, but pneumothorax occurred spontaneously also in three C cases.

Toxicity

Toxic effects of streptomycin therapy were observed in many patients, but in no single case did they necessitate cessation of treatment. For this reason and because toxic effects of this antibiotic have already been fully described by other investigators—e.g., Veterans' Administration (1947)—they will be mentioned here only briefly.

By far the most important toxic effect was the damage to the vestibular apparatus. Giddiness was a frequent first symptom; it was noticed by 36 of the 55 patients, and first appeared on sitting up in bed or turning the head suddenly. It appeared usually in the fourth or fifth week of therapy, and persisted for periods varying from one week to several months. Spontaneous nystagmus on lateral vision was another frequent sign of vestibular disturbance; blurring of vision was less common. Tests for vestibular dysfunction were not carried out in all centres with sufficient regularity and uniformity to permit analysis of grouped results, but it is possible to say that absence or reduction of caloric response was not found with the frequency reported in many American investigations, and that in some patients loss of response was temporary only. No standard functional tests at the end of treatment were performed; many patients are reported as having unsteadiness of gait, which improved gradually with visual compensation but remained a handicap in the dark. Possibly many of these patients retain a disability revealed in a dangerous ataxia on such occasions as walking downstairs in the dark, crossing a congested street, or walking in a moving train. It is highly desirable that standard tests be adopted for assessment of vestibular dysfunction.

No loss of hearing was reported, except for two cases of high-tone deafness. Many patients suffered from nausea and vomiting, symptoms which were often relieved by antihistamine therapy. Albuminuria and casts in urine, raised blood urea, pruritus and urticarial rash, eosinophilia, "yellow vision" after injection, and circumoral numbness are among other transient effects reported. All subsided spontaneously—i.e., without stopping treatment.

Bacteriology

(1) Bacterial Content of Sputum

Sputum was tested by direct-smear examination and by culture; where there was no sputum, material from laryngeal swab and/or gastric lavage was cultured. Examinations were done on admission and again at intervals of not more than one month.

In Table XIII the results in the third month and at the end of six months are related to the results on admission. Results of direct smear are recorded as "strongly positive" where one or more acid-fast bacillus per 1/12 in. (0.2 cm.) field was seen or where the result was recorded as +++ or ++; "weakly positive" includes results with less than one acid-fast bacillus per field or results recorded as +. For one hospital where only direct-smear examinations were done, and where degrees of positivity were not recorded, positive results in both groups have been tabulated in column 1, "strongly positive"; one C case and one S case (Nos. 3 and 107), positive on admission and negative to

TABLE XIII.—*Presence of Tubercle Bacilli*

Results on Admission	Total	Deaths	Results in Third Month			
			Direct Smear		Smear Negative Culture Positive	Culture Negative
			Strongly Positive	Weakly Positive		
S Cases:						
Smear strongly positive	40	0	16	12	10	2
Smear weakly positive ..	11	0	1	3	1	6
Smear negative, culture positive	3	0	1	0	0	2
C Cases:						
Smear strongly positive	29	5	19	3	1	1
Smear weakly positive ..	17	1	6	8	2	0
Smear negative, culture positive	4	0	1	1	2	0
			Results at End of 6 Months			
S Cases:						
Smear strongly positive	40	4	24	1	7	4
Smear weakly positive ..	11	0	3	3	2	3
Smear negative, culture positive	3	0	1	0	1	1
C Cases:						
Smear strongly positive	29	11	15	2	0	1
Smear weakly positive ..	17	3	4	7	3	0
Smear negative, culture positive	4	0	0	1	2	1

direct examination (no culture) at six months, have been excluded from the analysis; another (Case 62) has been excluded because no results were recorded for the third month.

Considering the results in the third month, one C case and 10 S cases were negative to all examinations for tubercle bacillus. Apart from these cases of "sputum conversion," six C cases and 23 S cases were positive at a lower level than on admission. The differences between the two series are significant. There is no doubt here of the pronounced effect of streptomycin on the tubercle bacillus.

The results at the end of six months also show a difference, though less marked, between the two groups; two C cases and eight S cases had become negative to all examinations. These final results signifying "sputum conversion" are based on repeated examinations, in most cases of sputum; the case with least satisfactory evidence had negative results from one gastric lavage and two laryngeal swabs. Besides these cases five C cases and 10 S cases were at six months positive at a lower level than on admission. Taking together cases becoming negative or positive at a lower level, the difference between the two series is significant.

In the S group the results are best in cases without gross cavitation; six of 23 became negative, compared with two of 31 cases with large or multiple cavities.

If in order to get an overall evaluation of changes we give a numerical score to each category of results (4=negative; 3=smear negative, culture positive; 2=smear weakly positive; 1=smear strongly positive; 0=death), the total in each group is as follows:

	On Admission	During Third Month	At end of Six Months
S cases ..	71	124	98
C cases ..	75	69	62

In the S group these results confirm the impression already gained of maximum improvement in the first months and subsequent deterioration.

The following numerical scores on the same basis are obtained from data for 51 of the S group analysed in greater detail (examinations for the C group were not frequent enough to provide comparable data).

Months after Admission:	0	1	2	3	4	5	6
Bact. "score"	66	111	115	127	105	104	94

This overall evaluation shows the marked improvement during the first three months, followed by a steep fall in "score" in the fourth month and further decline later.

(2) Streptomycin Sensitivity

Strains from 42 cases were tested for streptomycin sensitivity on primary isolation and during the course of treatment. Details of the technique adopted will be given in a subsequent report by the Pathological Subcommittee.

A. Degree of Sensitivity

All strains isolated before streptomycin therapy was begun showed sensitivity to the drug equivalent to that of the standard strain H37Rv (obtained from the American Depot, Trudeau Sanatorium, Saranac Lake); this was usually at a level of 0.1 to 0.5 μg. per ml., using the Tween-albumin medium.

Sensitivity after Start of Streptomycin Treatment.—(1) In one patient (Case 90) there was not full opportunity to detect streptomycin resistance, as all cultures were negative after the 59th day. (2) In six cases resistance did not emerge at a level above 10 times that of H37Rv. (3) In five cases strains were isolated which showed streptomycin resistance from 32 (one case) to 64 times (four cases) that of H37Rv. (4) In 17 cases resistance between 100 and 256 times that of H37Rv was demonstrated. (5) In 13 cases the resistance demonstrated was more than 2,000 times that of H37Rv; in four of these it was over 8,000 times.

Summarizing, strains with resistance over 10 times that of H37Rv were found in 35 of the 41 cases.

B. Time of Emergence of Streptomycin Resistance

In the majority it was not possible to detect with any great precision the date at which resistant strains could be first isolated, as specimens were not taken at frequent enough intervals. The date is taken as that midway between the date of the last sensitive culture and the date of the first resistant culture. In a few cases this interval was only a few days; in one it was 5½ months. Where it was possible to isolate strains at frequent intervals, it was seen that resistance rose rapidly to a maximum level at which it persisted subsequently with only minor fluctuations.

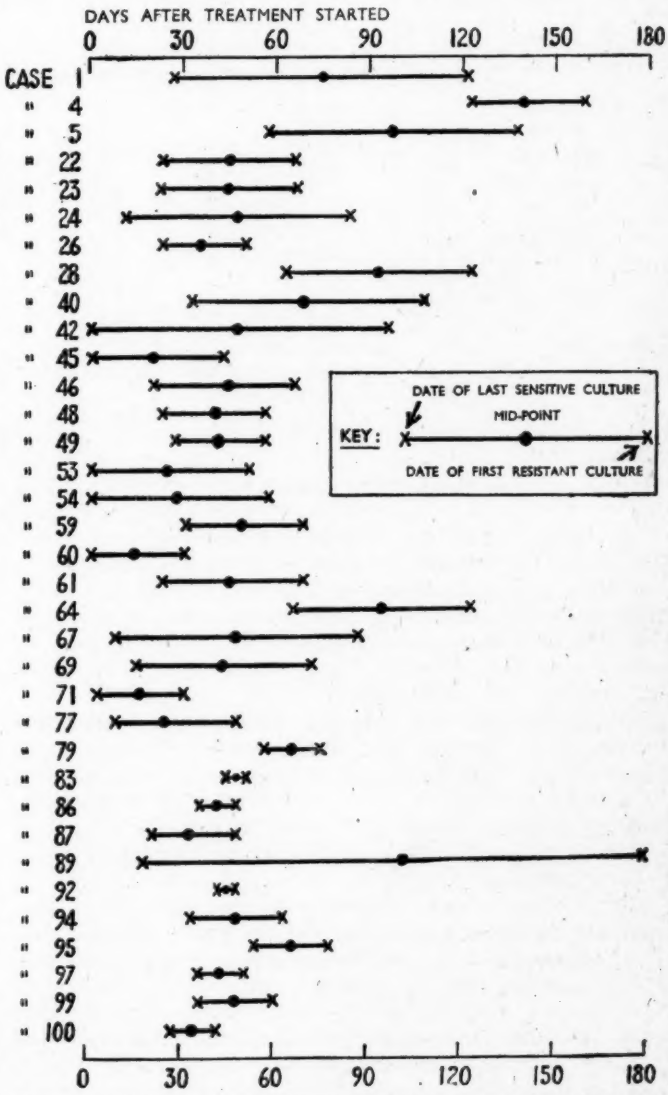

CHART V.—Showing date of emergence of streptomycin resistance (over 10 times that of H37Rv)

The results are shown in Chart V. Of 35 cases showing resistance over 10 times H37, this resistance emerged in five cases in the first month, in 21 in the second month, four in the third, four in the fourth, and one as late as the fifth month. Taking all observations, the mean date of

emergence of resistance is the 53rd day after starting streptomycin therapy. The median is the 45th day.

Results Related to Resistance Development

The results given in Chart VI raise an important point: the radiological results at six months compared with condition on admission seem to be related to the degree of

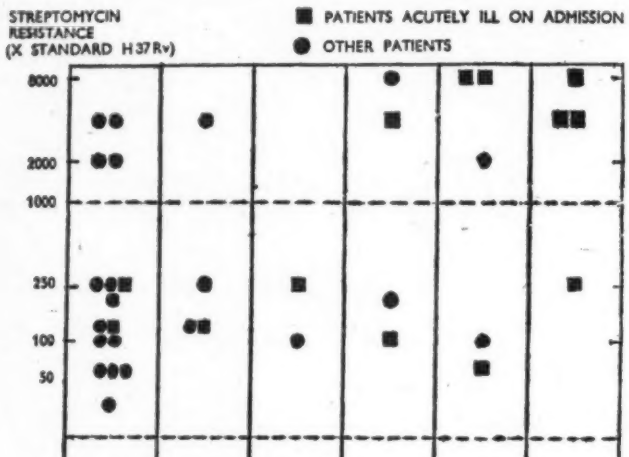

CHART VI.—Radiological assessment at six months related to degree of streptomycin resistance.

streptomycin resistance found during observation. Of six patients from whom strains isolated did not show resistance greater than 10 times that of the standard H37Rv, all had improved at six months. Twenty-two patients developed streptomycin resistance over 10 and less than 1,000 times H37Rv; five of them, or just under 1 in 4, had deteriorated at six months (one of the five had died). Of 13 patients in whom the drug-resistance developed was over 1,000 times H37Rv, eight or over one-half had deteriorated (three of the eight had died). The differences in results in the three groups are statistically significant.

If we consider not only the result at six months but deterioration at any time during the six months, it is interesting to note that the six patients who did not develop resistance over 10 times H37Rv improved throughout, without setback at any time in the six months.

Of the 22 cases with resistance 32 to 256 times H37Rv, deterioration occurred in six in the fifth and sixth months after continuous improvement in the first four months (but only two of these were worse at the end of six months than on admission); in two deterioration began after two months' improvement; one began to deteriorate in the third month, the condition having been stationary in the first two months; one died after continuous deterioration throughout. The remainder, 12 patients, did not deteriorate at any time.

In the cases with resistance over 1,000 times H37Rv, deterioration began earlier: within the first two months in four cases, in the third and fourth months after initial improvement in three cases, and only in the final months in two cases.

Before accepting degree of streptomycin resistance as a major factor in prognosis it is important to determine if among the cases with high streptomycin resistance there is a higher proportion of initially severe cases than in the others, as if so this might account for the worse prognosis. Six of the 13 patients from whom were isolated strains over 1,000 times more resistant than H37Rv were very acutely ill on admission (had high pyrexia and large or multiple cavities), compared with nine of the 28 other patients. The difference is small. Moreover, there is both in the patients very ill on admission and in the others the trend to bad prognosis with increasing levels of streptomycin resistance. Thus in those very ill on admission the proportion deteriorating was 0/2 where resistance was not more than 10 times H37Rv, 3/7 where it was more than 10 and not more than 1,000 times (one of the three died), and 6/6 where it was above 1,000 times (three of the six died). In the other patients it was 0/5 where resistance was not more than 10 times H37Rv, 2/14 where it was more than 10 and not more than 1,000, and 2/7 where it was over 1,000 times. However, while the trend to bad prognosis with increasing levels of drug resistance is seen in both groups, the trend is greater in the patients very ill on admission than in the others; there is a possibility of relationship between severe clinical condition and development of high degrees of streptomycin resistance. In conclusion, one can say that the results were outstandingly good in cases in which little or no drug resistance was demonstrated, but for the others it remains difficult to assess the relative importance and the interdependence of the two factors—clinical condition at start of treatment and degree of drug resistance developed during treatment.

Discussion

This planned group investigation has demonstrated both the benefit and the limitations of streptomycin therapy in pulmonary tuberculosis. The trial—the first controlled investigation of its kind to be reported—was designed to give a negative or affirmative answer to the question, Is streptomycin of value in the treatment of pulmonary tuberculosis? It was not designed to determine in what types of pulmonary tuberculosis streptomycin could be effective, nor to determine optimal dosage or duration and rhythm of treatment.*

Analysis of the results at the end of the first six-month period has shown that the course of bilateral acute progressive disease can be halted by streptomycin therapy; 51% of the streptomycin-treated patients showed considerable improvement radiologically when comparison was made with their chest radiographs taken on admission. That streptomycin was the agent responsible for this result is attested by the presence in this trial of the control group of patients, among whom considerable improvement was noted in only four (8%), and two of these four patients had improved only after collapse therapy. In other words streptomycin therapy was effecting what the patient's tissues alone could not do—checking the spread of the tubercle bacillus in one of its most favourable *milieux*.

Among the treated patients radiological improvement occurred most often in those who, though having extensive infection, did not have large or multiple cavitation. Nevertheless in one-third of those with gross cavitation considerable improvement also occurred, principally by resolution of recent infiltrative spread; some cases thus became suitable for collapse therapy. Streptomycin therapy alone did not lead to closure of large cavities.

The need of a control group in trials of a new drug for pulmonary tuberculosis is underlined by the finding that

*Since this investigation was begun a number of notable publications on the effect of streptomycin in pulmonary tuberculosis have appeared. As, however, the prime objective of the Medical Research Council trial was a comparison of treated cases with controls, other investigations have not been referred to here.

impressive clinical improvement was seen in some of the patients treated by bed-rest alone: 12 gained more than 14 lb. (6.35 kg.) in weight, and in 13 of 47 febrile patients the temperature was within normal limits at the end of six months. It was to be expected that in many of these patients with gross lesions who until recently had been at work the constitutional symptoms would be temporarily improved by bed-rest, although the lesions were so advanced that bed-rest alone could not be expected to effect corresponding improvement in the radiological picture. Nevertheless it should be noted that some radiological improvement was recorded in one-third of the C patients. The improvement in these patients was mainly among those least acutely ill on admission, and it is in this group that the treated series shows the least advantage over the control series. In such cases, with little or no pyrexia, relatively low sedimentation rate, and little cavitation, the patient's natural recuperative power added to bed-rest may in itself arrest the progress of the infection, and the advisability of using streptomycin in such cases may well be doubted. The major advantage is among the acutely ill patients. Although the only deaths that occurred in the S series were in this group, it is in these patients that the striking difference between the S and C series is most clearly demonstrated.

While stressing the good results in the streptomycin group, it is important to note, first, that no clinical "cures" were effected, and that only 15% were bacteriologically negative (to direct examination and culture) at the end of six months; and, secondly, that this trial presents at the time of writing only a short-term evaluation.* The major improvement in patients treated with streptomycin was seen in the first two to three months; in the latter half of the six-month period numbers of them began to deteriorate. Thus 21 S patients deteriorated radiologically in the fifth and sixth months, and four of them died. Streptomycin therapy had been stopped at the end of four months, and it is natural to ask whether the deterioration is attributable to stoppage of treatment. This seems unlikely for the majority; most had begun to deteriorate radiologically before the end of four months; only six of the 21 had improved radiologically throughout the four months, and two of these six had deteriorated clinically.

Strains of tubercle bacilli resistant to high concentrations of streptomycin were isolated by the end of the second month of treatment from most patients whose sputum was still positive; this fact may account for at least a part of the deterioration witnessed in treated patients. Strains showing streptomycin resistance over 10 times that of the original strain or of the standard H37Rv were isolated from 35 of 41 patients for whom data are available; in 13 of the 35 cases the strains had a resistance over 2,000 times that of the control organism.

Therapeutic results appear to be related to the degree of drug resistance developed; thus the best results were seen in cases in which little or no drug resistance was demonstrated, and the worst results were in the group of 13 patients from whom were isolated strains of tubercle bacilli with a drug resistance over 2,000 times that of H37Rv; at the end of six months three of the 13 had died and five were radiologically worse than on admission. The relation between a bad prognosis and a high degree of streptomycin resistance applies particularly to patients most acutely ill at the start of treatment. The numbers involved are small, but the differences between the groups at different levels of resistance are suggestive. Probably both initial severity of clinical condition and development of drug resistance during treatment are factors responsible for deterioration, and the two factors may be interdependent. Even with the aid of a powerful chemotherapeutic agent healthy tissue reaction on the part of the host is necessary for complete destruction of the invading parasite. It is reasonable to suppose that, where a high degree of streptomycin resistance is demonstrable by the method used (which is qualitative and not quantitative), this may have occurred by rapid proliferation of resistant strains in tissues that have a poor natural defence against tuberculous infection.

*An addendum gives the results at one year after admission to the trial.

On knowledge at present available, the development or emergence of streptomycin-resistant strains of tubercle bacilli is a fundamental factor to be taken into consideration when contemplating a course of streptomycin therapy. The technique of measuring sensitivity used in this investigation is so slow as to be of little immediate use in estimating, say at the end of one or two months of therapy, whether the course can be usefully continued or not. Organized investigations will be needed to determine whether emergence of streptomycin-resistant strains can be prevented by association of streptomycin with another drug or by a special rhythm of treatment. Until such time as this problem has been solved it seems fair to assume that after two to three months of streptomycin treatment in a patient with open pulmonary tuberculosis further treatment or a repeat course later is unlikely to be effective. Moreover, the possible dangers to the public health of dissemination of streptomycin-resistant strains, with the possible subsequent production of fresh cases (including cases of miliary or meningeal tuberculosis) which would not respond to streptomycin treatment, must be borne in mind.

One must add to this disadvantage of streptomycin therapy the information on the drug's toxic effects on the vestibular apparatus. These are frequent when the dose employed in this trial, 2 g. a day, is given; recent American reports indicate reduced toxicity with a dosage of 1 g. a day, but even then the effects are far from negligible.

These considerations must dictate a full measure of caution before prescribing streptomycin for any particular patient. They must be weighed in the balance against possible advantages of streptomycin therapy, particularly when contemplating its use for tuberculous lesions likely to improve by other known forms of treatment; and they render undesirable its administration for tuberculous lesions which, by reason of their age and pathological type, are unlikely to benefit by any form of chemotherapy.

The investigation reported here has demonstrated the value of streptomycin in one not very common form of tuberculosis. The type of result obtained indicates that the drug is probably of greatest value in cases of pulmonary tuberculosis in which the lesions requiring treatment are acute and of recent development. Its use may be recommended in acute contralateral spreads after artificial pneumothorax or after thoracoplasty. It probably has a place in the treatment of rapidly advancing pulmonary tuberculosis in which immediate collapse therapy would be dangerous or impracticable; in fact its most effective use may be in preparation of such lesions for collapse therapy. It has probably little place in the treatment of the more common chronic fibro-caseous forms of the disease. These conclusions are of necessity lacking in precision; much organized work is yet required to determine the precise indications of streptomycin and the best schemes of dosage in pulmonary tuberculosis.

Addendum

Before going to press it has been possible to collect data regarding the condition of each patient one year after admission to the trial. The data are based on a general

assessment by the clinicians concerned. Radiological evaluation by a panel was not possible, and therefore, although the data give a provisional impression of the course of the disease in these patients, the figures are not comparable with those based on independent radiological assessment, for example, in Table II.

TABLE XIV.—*Condition at 12 Months Related to Condition on Admission*

Group	Total	Improvement	No Change	Deterioration	Death
S	55 *100%*	31 *56%*	4 *7%*	8 *15%*	12 *22%*
C	52 *100%*	16 *31%*	5 *10%*	7 *13%*	24 *46%*

The difference in mortality between the two groups is statistically significant.

Summary

One hundred and seven patients with acute progressive bilateral pulmonary tuberculosis, unsuitable for collapse therapy, were studied in a clinical trial of streptomycin.

The supply of streptomycin available during the investigation was limited. The type of disease selected was one considered hitherto unsuitable for any form of treatment other than bed-rest. Bed-rest accordingly was the treatment given to one group of 52 patients (C), while 55 patients were treated with bed-rest plus streptomycin (S). Patients were assigned to one or the other group by random selection, and only after acceptance as suitable for the trial.

The period of observation for each patient, under conditions laid down for the trial, was six months.

S patients received 2 g. of streptomycin intramuscularly daily in four injections at six-hourly intervals. No toxic effects necessitated stopping treatment, but vestibular disturbance was common.

At the end of six months 7% of S patients and 27% of C patients had died. Considerable improvement radiologically was noted in 51% of S cases and 8% of C cases. Slight or moderate improvement was noted in 18% of S cases and 25% of C cases. Apart from those who died, deterioration was seen in 18% of S cases and 34% of C cases.

The main difference between S and C series is among the patients clinically acutely ill on admission: thus, among patients having on admission evening temperatures of 101° F. (38.3° C.) or over, 13 of 24 S patients and two of 19 C patients showed improvement radiologically.

More S patients than C patients showed clinical improvement, but the difference between the two series is smaller than in respect of radiological changes.

Improvement in S cases was greatest in the first three months. After the end of this period many S cases began to deteriorate.

At the end of six months examinations for tubercle bacilli were negative in eight S cases and two C cases. The best results in S cases were seen in the first months of treatment.

Results of tests for streptomycin sensitivity of infecting strains are given for 41 cases. In 35 cases tests revealed *in-vitro* resistance from 32 to over 8,000 times that of the original strain or the standard H37Rv. In most cases streptomycin resistance emerged in the second month of treatment. It seems probable that streptomycin resistance is responsible for much of the deterioration seen in S cases after first improvement.

An addendum gives the results at one year after admission.

The work of this investigation fell particularly heavily on the nursing staff and laboratory technicians of the centres concerned, and grateful acknowledgment is due to them for their assistance throughout the trials.

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SUDDEN DEATH DUE TO EPENDYMOMA OF CEREBELLO-PONTINE ANGLE

REPORT OF TWO CASES

BY

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Sudden death has been described in many cases of subtentorial tumours, but such an occurrence is almost invariably preceded by symptoms of raised intracranial pressure severe enough to induce the patient to seek medical advice some months before death. In the first case described here the patient gave a history of mild illness for only two days, whilst in the second case the patient continued at work until the day before his death. The presence of an intracranial tumour was not suspected during life in either case.

Bailey, Buchanan, and Bucy (1939) point out that sudden death may occur in cases of ependymoma of the fourth ventricle, but they describe such an occurrence only after lumbar puncture or manipulations of the head. Neither of these procedures was carried out in the present cases.

Case 1

A girl aged 2 was in good health until two days before her death, when she appeared unwell and was constipated. She was taken to her doctor, who prescribed an aperient; next day she was better and able to take her food satisfactorily. On the following day, however, she suddenly had a fit, made a choking noise, and died in a few minutes.

At necropsy a firm, pale, lobulated tumour with a smooth surface and crenated edge and measuring 4.3 by 3.7 cm. was found on the inferior surface of the left lobe of the cerebellum, being related laterally to the medial surface of the left petrous bone. Superiorly the tumour reached and compressed the lower border of the pons, and inferiorly the medulla and the upper part of the cervical cord were partially encircled and thrust towards the right. The tumour reached a point 4 cm. below the lower border of the pons and 1.2 cm. to the right of the midline. The left cerebellar hemisphere was compressed.

The left eighth cranial nerve ran into the mass, whilst the left vertebral artery, which lay on its surface, was partially embedded in its substance. The whole was covered by the arachnoid mater, which could be moved freely over it. There was evidence of raised intracranial pressure, with flattening of the convolutions of the cerebrum and bulging and thinning of the infundibulum, but the lateral ventricles appeared to be normal in size. No other lesions were found post mortem.

Histologically, the tumour had the appearance of an epithelial type of ependymoma (Fig. 1). The cells composing it contained round or oval nuclei showing rather coarse chromatin granules. Many of these cells formed canals with empty lumina lined by a single layer of cuboidal or columnar epithelium with basal nuclei, whilst others were arranged in rosettes around coils of cell processes. There was a complete absence of a basement membrane separating the rosettes from the surrounding stroma. The blood vessels were thin-walled, and in some areas the tumour cells were arranged around them, their processes extending to the vascular endothelium. The stroma consisted of a fibrillary network.

Case 2

A boy aged 16 had suffered from headaches and occasional vomiting for two months but remained at work until the day before his death. He then complained of very severe headache and went to bed, where he was found dead the following day.

At necropsy a firm lobulated swelling, similar to that seen in Case 1, and measuring 6.2 by 4 cm., was found lying in the right cerebello-pontine angle on the inferior surface of the right cerebellar hemisphere. Superiorly it compressed the pons

Fig. 1.—Section from tumour of Case 1, showing epithelium-lined canals. (× 210.)

and extended over the right middle cerebellar peduncle to a point 0.8 cm. above the lower limit of the pons, whilst inferiorly it passed through the foramen magnum and partially encircled the cervical cord, reaching a point 0.7 cm. to the left of the midline. The tumour pressed upon the medulla, displacing it to the left, and compressed the right cerebellar hemisphere. The right vertebral artery lay between the tumour and the overlying arachnoid mater, whilst the right eighth cranial nerve was embedded in the substance of the mass. No other lesions were found post mortem.

Histologically (Fig. 2) the tumour was much more cellular than that described in Case 1. The cells resembled astroblasts,

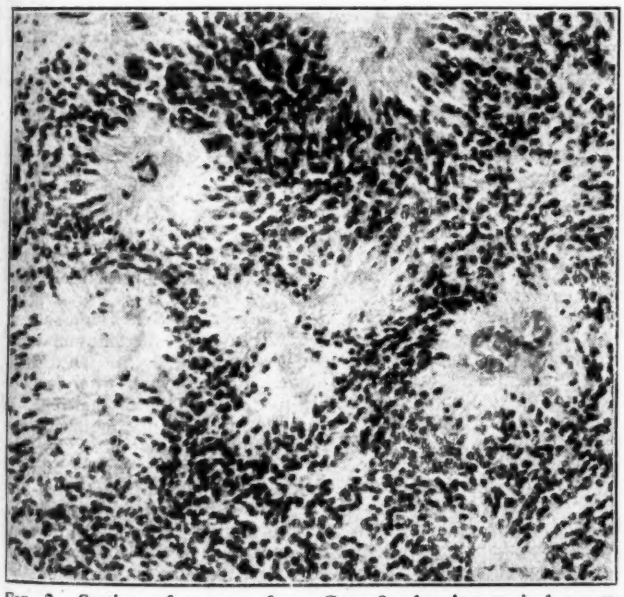

Fig. 2.—Section of tumour from Case 2, showing typical rosette formation. (× 150.)

but the nuclei were round or oval, with a coarse chromatin network. In many areas they were arranged in rosettes around coils of fibrils, sometimes with a thin-walled blood vessel in the centre. In no parts could epithelium-lined canals be found. This is the histological picture of a cellular type of ependymoma.

Comment

These two cases showed ependymomas of similar macroscopic appearance, Case 1 being of the epithelial type and Case 2 of the cellular type (Kernohan and Fletcher-Kernohan, 1937). Each tumour occupied one cerebello-pontine angle and exerted pressure on the pons, medulla, and cerebellum.

Ependymomas most often arise in the fourth ventricle, and their tendency to extend into the cerebello-pontine angle has been pointed out by Courville (1945). Having reached the basal cistern they may spread widely over the inferior surface of the cerebellum and around the medulla and cervical cord until their size is such as to cause pressure and give rise to symptoms. In a small percentage of cases sudden death may occur. When such a catastrophe as haemorrhage into a tumour occurs the cause of death is obvious (Wedd, 1942), but in the majority of cases of subtentorial tumours it is obscure.

Craig (1933) has stated that sudden collapse in patients with cerebellar tumours is usually due to respiratory failure, and both he and Werden (1939) describe the successful removal, under artificial respiration, of such tumours when acute respiratory failure had occurred. On account of the anatomical positions of the neoplasms described in this paper, showing definite pressure upon the medulla and upper cervical cord, the addition of a moderate rise of intracranial pressure could easily precipitate acute respiratory failure. There is, however, no evidence in these cases of a definite cause for sudden raising of the pressure.

Grant, Webster, and Weinberger (1941) point out that convulsions are often seen in addition to the usual signs of raised pressure, and Webster and Weinberger (1940) conclude that these are due to cerebral anaemia.

It is possible that a sudden strain may in some way cause an increase of intracranial pressure great enough to give rise to a convulsion. It is perhaps significant that the only symptom of ill-health in Case 1 was constipation, and this may have predisposed to the convulsion which immediately preceded death.

Typical cerebellar fits, characterized by head retraction, extended arms and legs, irregular pulse, and pyrexia with clouded consciousness, are believed to be due to compression of the bulbar centres (Bailey, 1933). It seems possible that such a fit was the explanation in these cases, although usually there is a history of similar convulsions which become longer in duration and more severe until one finally ends in death.

Summary

Two cases of sudden death due to ependymomas in the cerebello-pontine angle are described.

Acute respiratory failure, cerebral anaemia with convulsions, and cerebellar fits are discussed as possible causes of death.

I am indebted to Professor J. Gough for his criticism and permission to publish these cases, and to Mr. G. R. Armstrong and Mr. J. P. Napper for their technical assistance.

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SKIN TESTS FOR SENSITIVITY TO LIVER

BY

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It is well recognized that patients maintained on parenteral liver therapy may develop sensitivity to liver extract. Intradermal tests are usually employed as diagnostic aids in this condition, but there is a lack of uniformity in the interpretation of them. McSorley and Davidson (1944) recommend the use of 0.05 ml. of undiluted liver extract and accept a weal of over 15 mm. in diameter appearing in 15 to 30 minutes as a positive response, but they found that 16 out of 52 patients maintained on parenteral liver therapy were positive to a skin test although tolerating their injections without clinical reactions. Allin and Meyer (1940) observed weals in 13 out of 14 normal subjects given 0.05 ml. of liver extract intradermally, and they suggest that only a weal with pseudopods should be accepted as a positive response. Other authors have observed that patients with clinical sensitivity to liver extract usually show a definite weal and flare after an intradermal injection of a 1 in 1,000 dilution of the extract (Feinberg *et al.*, 1943 ; Bauer *et al.*, 1947).

The present investigation was undertaken in order to try to assess the value of skin tests in the recognition of sensitivity to liver.

Results

The cutaneous reactions of a group of patients undergoing maintenance treatment with liver injections were compared with those of a "control" group of patients suffering from a variety of diseases. The age and sex distribution of the two groups was strictly comparable, and the same highly purified extract of liver was used for therapy and for the intradermal tests.

All patients were given 0.05 ml. of liver extract intradermally and the readings were taken after 10 to 15 minutes, since it was found in some cases that the weals tended to become less distinct after 15 minutes. It was impossible to record the results in quantitative terms, for the size of the flare was of little significance ; the intensity and regularity of the weal seemed to be of greater importance than its actual diameter. The responses were therefore graded as follows: (1) a flare only ; (2) a doubtful weal—i.e., a flare with raised central area which blanched when the skin was stretched ; (3) a classical weal and flare ; and (4) a weal with pseudopod formation. Definite weals were produced not only in 9 out of 11 patients receiving liver but also in 9 out of 11 controls, and the reactions were no more intense in those receiving liver (Table I).

TABLE I.—*Results of Tests with 0.05 ml. of Liver Extract*

	Intensity of Reaction			
	Grade 1	Grade 2	Grade 3	Grade 4
Control group	—	2	7	2
Patients receiving liver ..	—	2	8	1

Three separate groups of patients were then tested with serial dilutions of liver extract in normal saline. Each of these groups was subdivided into patients receiving liver injections and "normal" controls, but since there was no significant difference between these subgroups the results have been pooled in Table II. Definite weals were observed in 8 out of 14 subjects tested with a 1 in 10 dilution of liver extract, in 1 out of 26 tested with a 1 in 100 dilution, and in none of 17 tested with a 1 in 1,000 dilution.

TABLE II.—*Results of Tests with Dilutions of Liver Extract*

Dilution	Intensity of Reaction			
	Grade 1	Grade 2	Grade 3	Grade 4
1 in 10	2	4	8	—
1 in 100	23	2	1	—
1 in 1,000	16	1	—	—

While carrying out these experiments I have had the opportunity of doing skin tests on three patients with clinical manifestations of acquired sensitivity to liver. All three reacted with the formation of a definite weal when given 0.05 ml. of a 1 in 100 dilution of liver extract, and in two of them weal formation was observed with a 1 in 1,000 dilution.

Discussion

The diagnosis of acquired sensitivity to liver extract should be made mainly on clinical evidence. Skin tests are of secondary importance: they may show only approximate correlation with the severity of the symptoms (Bauer *et al.*, 1947), and cases have been reported in which they were negative at the time of the first reaction and became positive later (Delikat, 1943 ; McSorley and Davidson, 1944). Positive reactions usually persist in patients who have been successfully desensitized (Feinberg *et al.*, 1943), and this was observed in one of the cases recorded above.

There are patients, however, who describe vague and indefinite reactions after liver injections, and it is often difficult to know how much significance should be attached to their stories. In such cases the result of an intradermal injection of 0.05 ml. of a 1 in 100 dilution of liver extract may be of considerable assistance in diagnosis.

Conclusion.—Most normal people respond with a typical weal and flare to the intradermal injection of undiluted liver extract. It should not be concluded that a patient is sensitive to liver unless such a reaction is obtained with a dilution of purified extract of at least 1 in 100.

I am grateful to Professor L. J. Witts for his advice.

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The Ministry of National Insurance states that in the first three months of the National Insurance Scheme 293,000 claims for maternity benefit have been made and that they are coming in at the rate of about 18,000 a week, but some mothers are losing money because they make their claims too late. The Ministry recalls that there are three kinds of maternity benefit. First there is a grant of £4 to help towards the usual expenses of having a baby. The grant can be claimed seven weeks before the birth is expected and must be claimed not later than three months after the event. Then there is an attendance allowance of £1 a week for four weeks after confinement for the additional help needed in the home during that time. It must be claimed within ten days of the birth. If the mother is not well enough someone else can claim for her and if necessary sign the form. The grant and the attendance allowance can be claimed either on the mother's own insurance or on her husband's, but not on both. To those mothers who have been in work or registering at an employment exchange over the year ending six weeks before they expect their baby a maternity allowance may be paid instead of the attendance allowance. This allowance is 36s. a week for the 13 weeks beginning six weeks before confinement, provided that the mother gives up her work for this period. It should be claimed seven weeks before the week in which the baby is expected. If the claim is not sent in six weeks before the expected date of confinement, part of the allowance may be lost. Fuller details of these benefits and the conditions on which they are paid are given in Leaflet N.I.17, and every expectant mother should get a copy from her maternity clinic. The leaflet can also be had at any local National Insurance Office, and inquiries about maternity benefit should be sent there.

HEREDITARY HAEMORRHAGIC TELANGIECTASIA

BY

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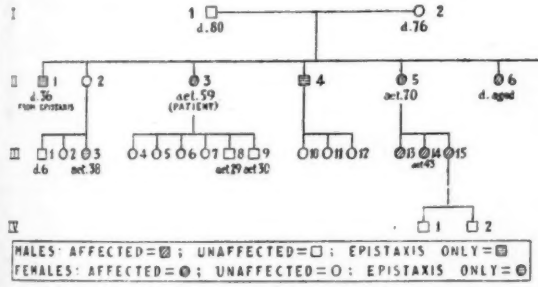
Hereditary haemorrhagic telangiectasia, sometimes known as the Osler–Rendu disease (Rendu, 1896 ; Osler, 1901), is a well-recognized but somewhat rare condition whose essential features are defined by its name. The characteristic lesions are telangiectases, or aggregations of dilated small vessels, initially minute but gradually increasing in size, scattered over the skin of the face and arms and the mucosa of the nose, mouth, and pharynx. They are also recorded as occurring at less usual sites such as the bronchial tree and the bowel. These defects are not present at birth but develop later, often in middle life. Their constituent vessels are formed by a single layer of endothelium and tend to bleed, most commonly in the form of recurrent epistaxis, to such an extent as to produce a severe microcytic anaemia or even death. Usually haemorrhage or anaemia brings the patient to the doctor. The familial incidence is very pronounced and is considered to show inheritance of the trait as a Mendelian dominant. The following pedigree is an addition to the available data.

Case History

The patient (II 3), a woman aged 59, came to hospital feeling "run down." She was very pale and gave a history of repeated severe bleeding from the nose. Examination of the blood showed : haemoglobin, 30% (Haldane) ; red blood cells, 3,570,000 per c.mm. ; colour index, 0.4. No other abnormality was at first obvious, but, when her colour had been a little restored by the administration of iron, telangiectases were clearly visible on the face and arms, in the conjunctiva of the right eye, and in the mucous membrane of the mouth and nose. She stated that she had only recently noticed these spots, but questioning revealed that three of her sisters (II 5, 6, 7) had similar facial blemishes. Two of these had died in old age, and



the third, aged 70, could not come for inspection. Her two brothers (II 1, 4) had severe epistaxis, one of them dying from this cause at the age of 36, which marks him (II 1) as a probable sufferer. The remaining sibling is unaffected. The patient's own six children do not yet show the condition, but since the eldest is only 30 they have time to develop it. Among her nephews and nieces a family of three sisters are all affected (III 13, 14, 15). One (III 13) has emigrated to Canada, where she is shown at clinical meetings as a case of a rare disease with "spots" on the face, presumably of the family complaint. Another (III 14) came to see me by invitation and showed typical telangiectases on the face and arms, but has not yet suffered from bleeding. The third (III 15) has not been able to attend, but is said to have identical lesions. The descendants of the patient's unaffected sibling are also of interest. One (III 3) has severe epistaxis at the age of 38 ; another (III 1) died suddenly at the age of 6, bringing to mind the recorded instances of intracranial haemorrhage in early life in these families which have led some writers (Goldstein, 1921 ; Mekie, 1927) to postulate cerebral telangiectases.

Discussion

Interest has been aroused in the haematology of this condition by Penfold and Lipscomb's (1943) report of a family in which hereditary haemorrhagic telangiectasia was associated with elliptocytosis of the red cells. Elliptocytosis is a feature of primitive marine vertebrates, and these authors put forward the interesting hypothesis that both abnormalities represent a harking back to an amphibian ancestor in which skin and oro-nasal mucosa have a respiratory function and are therefore highly vascular. I am indebted to Dr. R. H. Trinick, of the South London Blood Supply Depot, for examining my patient's red cells for elliptocytosis, which he reports to be absent.

Another recent report (Singer and Wolfson, 1944) describes a family affected by hereditary haemorrhagic telangiectasia in which all three cases examined were unusual in having strongly positive tourniquet tests. This led the authors to regard the disease as one of a group of "capillary heredopathies," the other members being hereditary familial vascular purpura and pseudohaemophilia. In the present case the tourniquet test, as it is usually described, was negative.

A recent introduction in the therapeutic field—rutin—has been claimed as valuable in preventing bleeding from the telangiectases by virtue of its beneficial effect on capillary fragility. This substance is a flavone glucoside allied to hesperidin and derived from *Fagopyrum sagittatum*. It was tried in the present instance in doses of up to 40 mg. three times a day for periods of a month at a time, but over a year there was no difference between the periods when rutin was taken and when it was not. Attempts at cautery of the nose have met with the usual rather disappointing results. Plugging has not yet been necessary ; the use of oxidized cellulose gauze has been recommended in this connexion (Kennedy, 1947). In my patient an adequate blood count is being maintained (latest haemoglobin, 90%) by the administration of iron—one "fersolate" tablet thrice daily. She therefore represents the middle range of an abnormality the severity of which varies from complete harmlessness to a cause of early death.

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The Ministry of Health, after consultation with the National Pharmaceutical Union and the Association of Executive Councils, has prepared a model scheme for testing the quality and amount of drugs and appliances supplied by chemists. It is proposed that England and Wales will be divided into six divisions, in each of which an analyst will work under contract with the executive councils in the division. Appliances will be tested by the Testing House of the Manchester Chamber of Commerce. When a test is to be carried out the clerk of the executive council will arrange for an official prescription to be written in duplicate and signed by a medical practitioner on the council's list; the practitioner will not be told the name of the chemist to whom the prescription is to be presented for dispensing. An agent of the executive council will present the prescription, and when it is dispensed he will tell the chemist that it is required for testing. The certificate of analysis given by the analyst or by the Testing House will be considered by the chairman or deputy chairman of the Pharmaceutical Service Committee and a registered pharmacist member of the committee. If they agree that no further action is required, the chemist will be informed that he may forward the prescription to the pricing bureau for pricing. If they consider that further action is warranted, the matter will stand referred to the Pharmaceutical Service Committee, which will investigate it as if a complaint had been made against the chemist in respect of an alleged failure to comply with his terms of service under Para. 2 of Regulation 4 of the National Health Service (Service Committees and Tribunal) Regulations, 1948.

INTUSSUSCEPTION IN ADULTS DUE TO CARCINOMA OF THE COLON

BY

R. A. C. OWEN, M.B., Ch.M., F.R.C.S.

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Intussusception in adults from any cause is rare, and cases due to carcinoma of the colon seem to be extremely rare. A search of the literature of the past 10 years reveals only two cases associated with a carcinoma of the colon. Rose (1945) described a case of intussusception of the descending colon due to a polypus with a near-by, but apparently unrelated, carcinoma of the colon. Iason (1945) described a case of intussusception of the transverse colon due to a carcinoma. Two further surveys dealing with this subject may be quoted to illustrate the rarity of the condition. Eliot and Corscaden (1911) collected up to that time 300 cases of intussusception in adults, only 20 being definitely due to carcinoma. Christopher (1936) could find only 10 cases of intussusception due to carcinoma since Eliot and Corscaden's paper. In view of this, and because they show other unusual features, the following two cases are recorded.

Case 1

A woman aged 72 was admitted with a history of colicky abdominal pain, diarrhoea, and the passage of blood per rectum for the past two weeks.

On examination she was seen to be a thin frail old lady with evidence of recent loss of weight. There was no abnormality detected on abdominal examination. Rectal examination revealed a typical sausage-shaped intussusception which had almost reached the anal orifice, and hence a diagnosis of chronic intussusception of the large bowel was made.

Operation.—Spinal analgesia was used. The abdomen was opened by a lower midline incision. An intussusception of the pelvic colon into the rectum was found. Reduction was, from the first, difficult, but was partially achieved with the aid of an assistant exerting pressure on the apex through the anal orifice. An impasse was then reached, as no further reduction seemed possible. On increasing the reducing force, signs of splitting of the bowel appeared, and as no other means was possible the split was enlarged and complete reduction was achieved. It was now found that at the apex of the intussusception, in the middle portion of the pelvic colon, there was a small annular carcinoma. The split in the bowel was below this in the upper part of the rectum. The condition was further dealt with by excising the portion of the bowel containing the carcinoma and the split. Continuity could not be re-established and so the proximal end was brought out of the left inguinal region to form a permanent colostomy and the lower end was closed with two layers of sutures as in Hartmann's (1923) operation for removal of a carcinoma in the recto-sigmoid region. The rest of the abdomen was not explored because of the danger of disseminating septic material. The wound was closed without drainage.

Recovery was uneventful, and the patient was discharged on the 42nd post-operative day. The delay in her discharge was due to difficulty in obtaining a colostomy belt. The growth was reported as being a mucoid carcinoma. When last seen, almost exactly two years after operation, she was in good health and without any evidence of recurrence of the growth.

Case 2

A man aged 68 was admitted with a history of two weeks' constipation, colicky abdominal pain, and the passage of blood per rectum.

On examination he was seen to be a well-built man in fairly good general condition. Abdominal examination revealed considerable generalized distension and an increase in peristaltic sounds on auscultation. On rectal examination a typical intussusception with a papilliferous carcinomatous mass at the apex was found. It had reached as far as the lower part of the rectum. A diagnosis of chronic intussusception of the large bowel due to a papilliferous carcinoma was made.

Operation.—Spinal analgesia was used. The abdomen was opened through a right lower paramedian incision. It was found that almost complete reduction of the intussusception had occurred : the cause of this is discussed below. A small knuckle of bowel was still invaginated and reduction was completed easily. It was now found that the intussusception was of the pelvic colon, which was very mobile, and the papilliferous carcinoma could be palpated in its middle portion. There was no evidence of secondary deposits in the liver or peritoneum. The condition was dealt with by resection of the colon containing the carcinoma, together with about 2½ in. (6.25 cm.) of normal colon on either side, by Paul's method. The double-barrelled bowel ends were brought out of a separate incision in the left inguinal region and Paul's tubes were inserted into the open ends.

Examination of the removed specimen showed a papilliferous carcinoma arising from an area about 1½ in. (3.75 cm.) in diameter in the middle of the loop of removed bowel. Microscopically it proved to be an adenocarcinoma.

Recovery was uneventful. The spur of the colostomy was crushed after an interval of three weeks, and the colostomy was finally closed at a second operation 10 weeks after the first. The patient was discharged 12 weeks after the original operation.

An interval of only seven months has elapsed since operation, but when last seen he was very well, with no evidence of recurrence. He had a slight tendency to constipation, but usually had a daily motion with the help of mild laxatives.

Discussion

Diagnosis.—This presented no difficulty in either case, as the intussusception was easily palpable on rectal examination ; in fact, in both cases it had nearly reached the anus. The presence of a carcinoma in Case 1 was not suspected until the abdomen had been opened and reduction of the intussusception had been completed. The carcinoma in Case 2 was readily palpable, and hence was diagnosed as the cause of the intussusception before operation.

Methods of Operation.—As this condition is of necessity associated with a long and mobile pelvic colon, Paul's method of resection of the growth would appear to be satisfactory—as in Case 2—and is particularly useful in the old patient who would not stand a more extensive removal. It has the advantage of resection of the colon combined with a colostomy in one procedure, and continuity of the colon can be re-established later without any further major operation. This method could not be used in Case 1 because of the splitting in the region of the pelvi-rectal junction, otherwise it would probably have been the method of choice.

Results.—The unexpected good result in Case 1 was both surprising and gratifying. In spite of the inevitable peritoneal contamination convalescence was uneventful. It is unfortunate, however, that continuity of the colon could not be re-established. The partial reduction of the intussusception which occurred in Case 2 was an unexpected find at operation. The cause could not be determined with certainty, but was probably due to a series of enemata which the patient received before operation. If this is so, it is interesting in view of the fact that this method of treatment of any intussusception has been advocated. It seems, however, that it could succeed only in intussusceptions of the distal colon.

I wish to thank Dr. H. H. MacWilliam, medical superintendent of Walton Hospital, Liverpool, for permission to publish these cases.

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Medical Memoranda

Two Unusual Cases of Abdominal Extrauterine Pregnancy

Two cases of abdominal extrauterine pregnancy are reported which were admitted to Mengo Hospital, Kampala, Uganda, within four months and present features worthy of record.

Case 1

The patient, a Muganda woman in the early twenties, had had a previous normal pregnancy. During antenatal observation the pregnancy appeared normal, the foetal position was left occipito-anterior, the head above the brim of the pelvis, but a small hard mass low down on the right side of what was thought to be the enlarging uterus was noted and presumed to be a fibroid.

On April 15, 1946, when apparently at term, the patient was admitted to hospital, having taken a native drug popularly believed to induce labour. This drug, we have observed, usually causes abdominal distension and tonic contractions of the uterus. She appeared to be very ill and in severe pain, with a rapid pulse rate. The abdomen was distended and the uterus felt very hard and was tender. The foetal position was anterior and the foetal heart rate 120 a minute. The head was above the brim and the cervix was not taken up. She was treated expectantly with morphine. The pain decreased, and on April 29 the head was found to have entered the pelvis and was well below the mass felt on the right side. After a month, during which time she complained persistently of pain, the physical signs were unaltered. A medical induction on June 1 was unsuccessful. At her own request, and as her condition was deteriorating, laparotomy was performed.

At operation on June 5 the foetus was found lying free in an amniotic sac in the abdominal cavity. The presentation was cephalic in a completely occipito-anterior position. Some exertion was needed to disimpact the head from the pelvis. The child, slightly postmature and weighing 8 lb. 2 oz. (3.66 kg.), was delivered alive. The uterus was enlarged to the size of a 10-weeks pregnancy. Immediately after delivery there was a profuse haemorrhage from some detachment of the placenta, which was implanted on and received the majority of its blood supply from the ovarian pedicle and left Fallopian tube and was also adherent to the omentum and mesocolon. The haemorrhage was temporarily controlled by a piece of rubber tubing used as a tourniquet around the base of the placental attachment. As much of the placenta was removed as possible, but the membranes were left *in situ*. The abdomen was drained for 24 hours. The condition of mother and child was good next day, and they were discharged from hospital well some three weeks later.

It is clear that the initial error of diagnosis was caused by mistaking the fundus of the uterus for a fibroid. The position of the foetus being anterior, no limbs were palpable and the firm back felt like a uterus in tonic contraction. The pains must have been due to the "false" labour described in these cases. The descent of the head into the pelvis was at the time unmistakable and supported the view that pregnancy was proceeding normally.

Case 2

The patient was a Muganda woman aged about 20 on whom a caesarean section had been performed by one of us (W.R.B.) for disproportion. Following this she was febrile for the first few days of the puerperium and the wound in the parietes healed by second intention. The present pregnancy, her second, began about January, 1946, and was uneventful in the early months except for one week of peri-umbilical pain in June.

On Aug. 1 there was a sudden onset of pain in the morning and the patient was admitted to hospital the same afternoon. On examination a foetus was felt lying transversely. Pelvic measurements were small and the pains did not appear to be true labour pains. The patient was observed until Aug. 10, when a membrane puncture with a Drew-Smythe catheter was attempted but only blood was obtained.

On Aug. 14 a laparotomy was performed, as an extrauterine pregnancy was considered likely. On opening the abdomen a blood-filled bag of membranes presented, and on opening this a macerated foetus was extracted. A second bag was seen and a second foetus removed. The placentas and membranes were adherent to the under surface of the liver. The uterus had a rent on its anterior surface and was filled with blood clot, and a subtotal hysterectomy was performed. The two umbilical cords were tied and cut short. The placentas were left *in situ*. One placenta was noted to be partially separated, and it was thought that the blood clot in and around the uterus was caused by blood draining by gravity from this placenta.

Penicillin was given and the patient made a good recovery. On Aug. 30 a soft mass dull on percussion was noted on the left of the umbilicus. This gradually increased in size until on Sept. 23 it almost filled the abdomen. It was freely movable and was not tender. There was no fever or leucocytosis. The patient left hospital on Sept. 26, and when seen a month later the abdominal mass was unaltered and her condition good. She refused to undergo a further operation and has not yet been seen again. It was thought that the swelling was caused by autolysis of the placentas rather than infection.

Dr. J. N. P. Davies, of the Medical Laboratory, Kampala, kindly reported upon the foetuses and the uterus, and stated that the male twin was smaller and lighter than the female. The male twin weighed 5½ lb. (2.5 kg.) and was 15 in. (38 cm.) in length. It appeared to have no abnormality, but examination was not complete before the twins were claimed by the father. The female twin was 17 in. (43 cm.) long and weighed 6¼ lb. (2.8 kg.). The uterus measured 4 in. (10 cm.) from the cervix to the fundus and there was a tear down the anterior surface. The specimen was shown to Dr. Gerald Holmes of Mulaga Hospital, and it was agreed that the tear in the uterus was of long standing and that it was the old caesarean operation incision which had failed to close. In between the pregnancies it would have been sealed over by the peritoneum, and the most probable sequence of events was that the developing ova were initially intrauterine and, either because of direct attack on the peritoneal covering or more probably because of rising pressure, broke through into the peritoneal cavity and became implanted upon the liver and spleen. Pregnancy then proceeded uneventfully until a partial separation of one placenta caused bleeding and abdominal pain on the date that the patient was admitted to hospital.

Our thanks are due to Dr. J. N. P. Davies and Dr. G. Holmes, of the Colonial Medical Service, for their advice and comments.

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R. T. S. Goodchild, F.R.C.S.Ed., D.T.M.&H.

Intravenous Procaine in Transfusion

The veins are innervated and their calibre is regulated in the same way as the arterioles; they constrict during pressor reflexes and dilate during depressor reflexes (Wright, 1945). Humble and Belyavin (1944) found that venous spasm occurring in shocked patients could interfere seriously with attempts at transfusion.

In cases of shock developing during operation the rate of flow of the intravenous drip transfusion may often be observed to become very slow, or it may even cease as a result of constriction of the recipient vein. On numerous occasions in such cases the administration of a solution of procaine hydrochloride by injection into the tubing of the transfusion apparatus near the needle has led to a great increase in the rate of flow, although neither the pressure of the transfusion nor the adjustment of the stopcock has been altered. This result is presumably due to a local action of the procaine in relaxing the constriction of the vein, for a prior control injection of a similar volume of normal saline does not produce the effect.

The amount of procaine hydrochloride usually employed is 5–10 ml. of 1% solution; that such an amount may be safely administered intravenously has recently been shown by many workers (Lundy, 1942; Gordon, 1943; Allen, 1945). This injection may need to be repeated, as the duration of the effect varies from 10 minutes to an hour or more. Several examples are quoted in the Table.

Operation	B.P.	Rate of Drip Before Procaine	Rate of Drip 1 Min. After Procaine
Laparotomy	95/60	36 per min.	200 per min.
For coarctation of aorta	110/60	100 ,,	270 + ,,
Fractured skull	120/70	48 ,,	135 ,,
Combined excision of rectum	100/70	30 ,,	150 ,,
Repair of ventral hernia	100/60	40 ,,	250 + ,,
Hemicolectomy	60/40	10 ,,	200 ,,

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Reviews

HUMAN EVOLUTION

A New Theory of Human Evolution. By Sir Arthur Keith. (Pp. 451. 21s.) London: Watts and Co. 1948.

This book is a series of 41 essays, each more or less self-sufficient, but grouped round the central notion that until the last 8,000 years or so the human species has consisted of small highly isolated groups, and that the instincts or mental biases making for such isolation have been a major factor in human evolution. This theory is not strictly new, and unfortunately Sir Arthur has not taken full cognizance of the extensive practical and theoretical work of Wright and his associates in America on the very different course which evolution takes in a wide-ranging species as compared with one broken up into small groups. Nor does he refer to the researches of Dahlberg or the extent to which small groups are still reproductively isolated in rural Sweden. It is possible that he exaggerates the extent of the isolation between such communities. If the various tribes of Australia were fully isolated sexually the contour lines of blood-group frequencies found in that country by Wilson, Graydon, Simmons, and Bryce would be quite unintelligible. Above all, he may well be at fault in supposing that the competition between such units was primarily by war. One can wipe out a primitive tribe as effectively with infectious diseases as with machine guns. If I had to frame a theory of human evolution (which heaven forbid) I should lay very great stress on disease as a selective factor. Keith cites Vallois for the statement that 40% of Neanderthal skeletons are of individuals under 11 years old. Man could not live in dense communities till he had become able to resist crowd diseases to a great extent, and immunological progress may have been as important as moral and intellectual in rendering civilization possible.

Sir Arthur thinks that a "dual code" of behaviour—amity to one's own group, enmity to outsiders—is part of a man's nature, and that hence wars cannot be avoided. "To the ethically minded," he states, "the dual code is anathema." Now, I practise a dual code of sexual behaviour, one type being reserved for my wife, the other for the remaining females of our species. My tomcat Puma has a unitary code, but if I imitated him I should be anathema to the ethically minded. Amity for one's own group need not imply hostility to others, and in fact many primitive tribes are hospitable to strangers while practising a fairly rigid endogamy. Nor do I murder or rob women to whom I am not married.

I agree with Sir Arthur that primitive communities may be regarded as evolutionary units, and completely disagree with his view that modern nations can be so regarded. A small tribe without any natural selection progresses half-way to complete homozygosis—i.e., loses half its heterozygosis—in a number of generations about equal to the number of breeding members in it. Thus a small tribe can become genetically homogeneous in a few thousand years; a nation could not in a hundred million. Moreover, most nations are extremely labile. We have only to consider the changes in the frontiers of Europe in the last 80 years to see that nations are not biological units, and that it is most unlikely that they will last long enough to give rise to races, as Sir Arthur believes.

Unfortunately the essay on "The Machinery of Evolution" is one of the weakest in the book. For example, the hypothetical population described on p. 127 has no mortality between the ages of 15 and 35. For an appreciation of recent work on this question the reader will do better to study such a book as Huxley's *Evolution.* On the other hand, in Essays 20 to 30, in which Sir Arthur discusses the actual history of human evolution, he writes from very extensive knowledge. Whether or not the view put forward that man originated from *Australopithecus* or some related form and spread out from Africa be ultimately accepted, it must be very seriously considered. Whether the major human races have evolved in parallel for as long as Sir Arthur believes may be doubtful, but his arguments for his thesis are strong.

Nevertheless, I believe that one of the central theses of the book—namely, that "altruism signifies a complete abandonment of the evolutionary outlook" (p. 72)—is not only immoral but false. It may have been true in palaeolithic times; it is not true now. Those who practise altruism in our own society accumulate less money than the egoists. But the poor breed quicker than the rich. It is, as a matter of hard fact, the meek who inherit the earth. The same is true of nations. The Germans were persuaded by Hitler that a respect for other human beings was biologically unsound. They lost a great deal of population and territory as a consequence of this belief. So, I hope and trust, will other nations which may imitate them in the future. The physician is bound to be somewhat of an altruist, and should realize that, by and large, altruism is not only ethically but biologically sound.

In spite of all these criticisms I can only close by stating that I shall congratulate myself if I can write as interesting and provocative a book as this at the age of 82. Even those who disagree most with it will find in it a wealth of information, particularly on the older literature of the subject and on recent human palaeontology, which will hardly be discovered elsewhere.

J. B. S. Haldane.

GASTRITIS

Gastritis. By Rudolf Schindler, M.D., F.A.C.P. (Pp. 462; 96 figures. £2 10s.) London: William Heinemann (Medical Books), Ltd. 1947.

This is a companion volume to the author's handbook on gastroscopy. It is written as a result of his experience since 1920 and is based on studies of more than 2,500 cases which were considered to be examples of uncomplicated gastritis. No one has done more than Schindler to paint a complete picture of gastritis, and his views will be studied closely in Britain, where opinions which differ from his are widely held.

Schindler is aware of his critics, and because of them he writes: "Gastroscopy is a subjective method, the results obtained will and should be read with wholesome criticism, and only physicians who look through the gastroscope, not only occasionally, but often and routinely, will feel obliged finally to correct their laudable conservative attitude. Too few have time to do that. For that reason I have built this book around histopathologic pictures. Their study may convince the sceptic of the reality of the disease entity, chronic gastritis."

The pathological material was obtained at necropsy, from gastrectomy specimens, and in 15 cases from biopsies of the stomach wall during laparotomy for some other purpose. He discusses the results at length and illustrates them in nearly 100 photographs and photomicrographs. These undoubtedly show different appearances, but whether these are to be regarded as pathological variations or whether they come within the wide range of normality of the gastric mucosa is still subject for argument. In addition to the illustrations this important book contains a mass of evidence, argument, and counter-argument. The style is not always easy to follow, but it must be studied carefully by physicians and gastroscopists as well as by morbid anatomists.

Christopher Hardwick.

TAYLOR'S MEDICAL JURISPRUDENCE

Taylor's Principles and Practice of Medical Jurisprudence. Tenth edition. Volume I. Edited by Sydney Smith, C.B.E., M.D., F.R.C.P.Ed., D.P.H. With a complete revision of the Legal Aspect by W. G. H. Cook, LL.D., M.Sc.(Econ.), and of the Chemical Aspect by C. P. Stewart, Ph.D., M.Sc. (Pp. 723; 48 illustrations. £2 5s.) London: J. and A. Churchill. 1948.

Medical textbooks of to-day seldom attain the literary distinction which characterize the writings of the nineteenth century. The changing pace of life and more scientific method of study militate against it. It is the more remarkable, therefore, that for some 85 years, through changing editorship, Taylor has retained its reputation as a work of forensic reference for its compass, authority, lucidity, and fine literary style.

Sydney Smith, who has guided its destiny for the last 20 years—longer than any previous editor—has moulded this new edition with great success. His remarkable experience in the subject and his ability in assessing the qualities of scientific

evidence have added appreciably to its value to the medico-legal specialist, and he has wisely retained so far as possible the pithy style and forthrightness of Taylor in the innumerable case histories which illuminate the text. Revision has been extensive *pari passu* with the advances in scientific knowledge and changes in statutory law, and it is unfortunate that the appearance of this first volume should take place at the moment when such a vast body of statute as the Workmen's Compensation Acts gives way to the improvements of the National Insurance (Industrial Injuries) Act; the legal editor, Cook, may find some remedy for this in the production of the second volume. Such a comprehensive and authoritative book of reference cannot afford to be without it.

It would be invidious for any reviewer to comb the text for what he might regard as omissions of detail, but Professor Smith's enthusiasm and vigour are capable of infinite effort, and we should like to see something of the encephalogram, of the psychiatrist's views on sadism and masochism in relation to both crime and accident, on the identity of race from the skull, on explosive blast, the assessment of healed wounds, the newer work on contre-coup, the physics of electrocution—so many mere trivialities on which he could discourse to our advantage. There is of course no end to such demands. Taylor remains a remarkably comprehensive volume of reference, authoritative, lucid, and in a literary style which maintains the best traditions of medicine.

KEITH SIMPSON.

MEDICAL PAPERS

Anales de la Cotedra de Clinica Medica. By Dr. E. S. Mazzei. Volume 1 (1946). (Pp. 367; illustrated. No price given.) Buenos Aires: "El Ateneo." 1947.

This volume is not easy to review, since it consists of a number of articles on unrelated subjects, and a comprehensive survey would necessitate a dissection of each article in turn. Of the sixteen papers presented, eight are about pulmonary embolism; they are written by Dr. Mazzei in collaboration with two of his colleagues. They discuss the subject exhaustively, broadly classifying the cases into medical, surgical, and obstetrical, of which medical account for 25%, surgical 74%, and obstetrical only 1%. They consider treatment under three heads—prevention of venous thrombosis, prevention of emboli, and the measures to be taken once an embolus has occurred. Some of the prophylactic advice, such as abstention from tobacco for ten days before operation, seems to be of doubtful value; some, such as the condemnation of the classical Fowler position, recalls recent controversy in Britain; most of it is thoroughly sound.

Among other papers in this volume there is a short but lucid one on the mechanics of obstructive emphysema and its relation to localized bronchial narrowing, with consequent difficulty in expiration of air from the part of the lung distal to the partial block. Another paper, distinguished by summaries in good Spanish, fair French, and indifferent English, is a review of modern concepts of functional renal insufficiency. The authors of the other papers each capably discuss a subject; although they may add nothing new they maintain the general standard.

A. MORTON GILL.

The discoverer of streptomycin was the first in the field with a book on antibiotics written from a broad and philosophical rather than a clinical standpoint. The second edition of *Microbial Antagonisms and Antibiotic Substances*, by Dr. Selman A. Waksman (London: Geoffrey Cumberlege; 22s.) is much expanded in scope and usefulness, even though more still has happened since it went to press—chloromycetin, for instance, one of the most promising of the latest discoveries, is not mentioned. As a soil microbiologist the author is at home in the greatest natural field of antibiotic activity, and in an interesting chapter discusses the possibility of controlling plant diseases by introducing or encouraging micro-organisms antagonistic to plant pathogens in the soil. He presents in orderly form the mass of information which has been accumulated in the past few years about hundreds of antibiotic substances formed by various fungi and bacteria, the methods of detecting, extracting, and studying them, and their chemical structure and biological activities. Few of these have attained the status of chemotherapeutic agents; many never can, owing to toxicity or other grave defect; others have yet to be fully tested. To this remarkable new branch of science Dr. Waksman's book is a comprehensive and useful guide.

BOOKS RECEIVED

[Review is not precluded by notice here of books recently received]

Emergencies in Medical Practice. Edited by C. A. Birch, M.D., F.R.C.P. (Pp. 468. 25s.) Edinburgh: E. and S. Livingstone. 1948.

A manual of the treatment of medical emergencies.

Psychology and Mental Health. By C. W. Valentine, M.A., D.Phil. (Pp. 82. 4s.) London: Methuen. 1948.

An exposition for the layman.

Everyday Problems of the School Child. By A. H. Bowley, Ph.D. (Pp. 142. 7s. 6d.) Edinburgh: E. and S. Livingstone. 1948.

A book for teachers and parents.

Andreas Vesalius Bruxellensis. The Bloodletting Letter of 1539. By John B. deC. M. Saunders, F.R.C.S., and C. D. O'Malley. (Pp. 94. 21s.) London: W. Heinemann. 1948.

Translation of letter by Vesalius on phlebotomy, with annotations.

Minutes of the Dental Board of the United Kingdom. Vol. 26. (Pp. 99. No price.) London: Constable. 1948.

Also contains committee reports for 1947.

Tuberculosis in Childhood. By D. Stopford Price, M.D., and H. F. MacAuley, M.Ch., F.R.C.S.I. 2nd ed. (Pp. 219. 25s.) Bristol: John Wright. 1948.

A general account of its epidemiology, symptomatology, and treatment.

Infra-Red Irradiation. By W. Beaumont, M.R.C.S., L.R.C.P. 3rd ed. (Pp. 161. 8s. 6d.) London: H. K. Lewis. 1948.

A manual of treatment with infra-red rays.

Handbook of Medical Emergencies. By a group of Harvard medical students. (Pp. 106. 14s.) London: Geoffrey Cumberlege. 1947.

Notes on the treatment of emergencies, intended particularly for students and house-men.

Problems of Fertility in General Practice. By M. Hadley Jackson, M.B., B.S., D.R.C.O.G., and others. (Pp. 255. 17s. 6d.) London: Hamish Hamilton. 1948.

The authors discuss sexual difficulties, the investigation and treatment of infertility, the prevention of repeated miscarriages, and contraception.

Modern Methods of Infant Management. By W. R. F. Collis, M.A., M.D., F.R.C.P., F.R.C.P.I., D.P.H., and others. (Pp. 285. 17s. 6d.) London: Heinemann. 1948.

A practical manual on management of the newborn infant.

Adolescence. By C. M. Fleming, M.A., Ed.B., Ph.D., F.B.Ps.S. (Pp. 261. 16s.) London: Routledge and Kegan Paul. 1948.

An account of the mental development of adolescents.

First-Year Physiological Technique. By A. Comfort, M.B., D.C.H. (Pp. 84. 7s. 6d.) London: Staples Press. 1948.

An introduction to technique in the physiology laboratory

A Short History of Ophthalmology. By A. Sorsby, M.D., F.R.C.S. 2nd ed. (Pp. 103. 8s. 6d.) London: Staples Press 1948.

A general history from earliest times.

Fever and the Regulation of Body Temperature. By E. F. DuBois, M.D. (Pp. 68. 10s. 6d.) Oxford: Blackwell Scientific Publications. 1948.

A monograph on the regulation of body temperature.

Disorders of Sex and Reproduction. By A. P. Pillay, O.B.E., M.B., B.S. (Pp. 299. 18s.) London: H. K. Lewis. 1948.

The investigation and treatment of physiological and psychological disorders.

The Growth of a Profession. By J. H. Wicksteed, O.B.E., M.C.S.P. (Pp. 212. 6s.) London: Edward Arnold. 1948.

A history of the Chartered Society of Physiotherapists.

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STREPTOMYCIN IN PULMONARY TUBERCULOSIS

In few infections is it so difficult to assess the results of treatment as in pulmonary tuberculosis, with its varied clinical picture and unpredictable course. Remarkable recoveries can take place with no treatment except rest in bed. In the Medical Research Council's trial of streptomycin in pulmonary tuberculosis, the report on which is published in this issue, there was a satisfactory control series of patients; this made it possible for the first time to make a fair estimate of the effects of the drug in one form of the disease. The method of investigation is discussed in the next leading article. The trial was designed to do no more than answer the question, Is streptomycin of any value at all in pulmonary tuberculosis? Although no attempt was made to determine either the types of disease likely to respond most favourably or the most effective dosage of the drug, much valuable information beyond the limited scope of the inquiry has in fact emerged.

The type of disease chosen was "acute progressive bilateral pulmonary tuberculosis of presumably recent origin, bacteriologically proved, unsuitable for collapse therapy, age group 15 to 25 (later extended to 30)." The treated (S) cases received 2 g. daily of streptomycin divided into four 6-hourly doses. Most patients were treated for four months, but some of the earlier ones for longer periods up to six months. The control (C) patients were treated by bed-rest alone in the same hospitals and with the same regime as the S cases apart from streptomycin administration. Although a few of the C patients became suitable for various forms of collapse therapy (artificial pneumoperitoneum with phrenic paralysis in all but one case) before the end of the observation period, these measures were not thought to have had an appreciable influence on the progress of most of them during the course of the trial. Both S and C cases were observed for a period of six months from the beginning of the investigation.

The results were analysed by changes in the radiographic appearances. These were assessed by a panel of three without knowledge of whether the films being viewed were those of S or C patients. The overall results leave no doubt of the beneficial effect of streptomycin. Of 55 S patients four (7%) and of 52 C patients 14 (27%) died within the six months. This difference is statistically significant. Of the S patients 27 (51%) and of the C patients four (8%) were judged radiologically to have improved considerably. Assessment of the changes in successive two-month periods showed that the improvement in S cases could often be seen during the earlier months, while the improvement in some of the C cases tended to occur later. Analysis of the results according to the degree of illness of the patients on admission showed that the difference in response to treatment between the S and the C cases was very much greater in those patients who were more acutely ill with higher temperatures on admission to the trial. There was relatively little difference between the results in the S and the C patients whose maximum evening temperature during the first week did not exceed 99.9° F. (37.75° C.), the differences between the two groups as a whole being accounted for almost entirely by the more severely ill patients.

The extent of improvement in both S and C cases was greatest in those with no initial gross cavitation; of the 23 S patients without large cavities 17 improved considerably and none died. Streptomycin did not have a marked effect on the presence of tubercle bacilli in the sputum. Complete bacteriological information was available in 54 of the 55 S cases. Of these 54, four had died by the end of the trial; tubercle bacilli were found on direct examination of the sputum in 32 cases and by cultural methods in another 10. In only eight could bacilli not be found by any method, as compared with two of the C cases. There were no striking differences in the changes of weight between the two groups; in assessing the significance of this the gastric upset caused in many patients by the streptomycin must be taken into account. The condition of the patients in the two groups was reviewed by the clinicians in charge at the end of a year from the beginning of the trial. The differences between the two groups were then less evident than at six months. Twelve (22%) of the S cases and 24 (46%) of the C cases had died, while 31 (56%) of the S cases and 16 (31%) of the C cases had improved. The difference in mortality is statistically significant. The general impression derived from the study of the two groups is that the results from streptomycin treatment were best in those patients whose lesions were active at the beginning of treatment but had not yet formed cavities. Presumably these were the lesions which were truly of recent origin. When large cavities were present the results were not so good, and in less acutely ill patients the difference in progress between the S and the C cases was smaller.

The most important toxic effect was on the vestibular apparatus: giddiness was noticed by 36 of the 55 patients, usually in the fourth or fifth week of treatment. Nausea and vomiting occurred often, but these symptoms were often relieved by "benadryl." In no case did treatment have to be stopped because of toxic effects.

Complete information was obtained about the streptomycin sensitivity of the organisms isolated from 42 of the 55 treated patients. The sensitivity of all the strains isolated before treatment approximated to that of the standard H37Rv. In 35 of the 42 cases strains showing resistance 32 or more times that of H37Rv were isolated after treatment; in 13 of these the resistance was more than 2,000 times that of H37Rv. The time at which these resistant strains were detected was estimated as the midpoint between the times of isolation of the last sensitive strain and of the first resistant strain. The mean figure on this basis was the 53rd day after starting treatment. When frequent cultures were obtained it was found that resistance rose rapidly to a maximum level which was subsequently maintained. Comparison of the date of

appearance and degree of streptomycin resistance with clinical results brought out the fact that on the whole those patients from whom highly resistant strains were isolated early did less well than those whose organisms showed lesser degrees of resistance later. Seven patients whose organisms did not develop resistance over 32 times that of H37Rv improved steadily. The figures are not large enough to correlate the clinical results, the degree of streptomycin resistance acquired by the organism, and the other relevant factors such as the type of lesion present at the beginning of treatment.

This investigation has achieved its limited object by proving that streptomycin is of value in the treatment of acute forms of pulmonary tuberculosis. Many further problems remain to be solved, however, before the indications for the use of this new remedy in pulmonary tuberculosis can be regarded as firmly established. There are already enough favourable reports to justify the use of streptomycin in the treatment of ulcerative lesions of the main bronchi at the pre-stenotic stage where these are affecting prognosis. Its value in ulcerative tuberculous lesions of the larynx, pharynx, and tongue is also well established. Patients with old and apparently stable lesions who develop, while under observation, acute spread of the disease in previously unaffected parts of the lung may be expected to respond well, since they can be treated when the lesions are at the very earliest stage. Whether or not streptomycin should be used as a routine prophylactic against extension of the disease after surgical treatment for pulmonary tuberculosis remains to be seen. It is certainly of great importance to determine, for instance, whether streptomycin should be given prophylactically to patients undergoing thoracoplasty or whether it is better reserved for the treatment of the smaller number in whom the disease actually extends after operation. The answer to this question cannot be deduced *a priori*; even if patients treated prophylactically showed better immediate results, in the long run they might be worse off, since those among them who later had a recrudescence of disease suitable for streptomycin treatment might prove to be harbouring resistant organisms and to be no longer responsive to the drug. The question of the proper use of streptomycin as an adjunct to collapse therapy, both medical and surgical, must be settled.

Streptomycin resistance is perhaps the most important problem of all. From the point of view of the individual patient the probability that the organisms will develop resistance after a relatively short period of treatment means that a course of streptomycin may be effectual only once during possibly a long and chequered illness. From the point of view of the community there is the risk that patients with unsuitable lesions ineffectively treated may disseminate streptomycin-resistant organisms, so that an increasing number of new cases of all forms of tuberculosis may in future be found to be unresponsive to streptomycin. It therefore seems in the best interests both of the individual patient and of the community that streptomycin should be used for the treatment of pulmonary tuberculosis with a proper understanding of the difficulties and dangers and only when the indications for its use are clear. Streptomycin may, of course, be outmoded in the treatment of tuberculosis by new and more potent antibiotics. Even so, the enormous amount of work done upon it will not have been wasted. Laboratory and clinical techniques which have been evolved can no doubt be applied to the problems of other antibiotics, and the Medical Research Council's controlled trial will serve as a model for future investigations of substances introduced for the treatment of pulmonary tuberculosis.

THE CONTROLLED THERAPEUTIC TRIAL

The clinical trial of a remedy is as old as medicine itself. The idea of controlled investigation and statistical analysis is recent enough to call new. With the older hit-or-miss method the patient was treated, and subsequent observation showed with what result. If the patient—or patients—died, or at least failed to get well, the results that flowed from the remedy were unequivocal. It is when the patients, or anyway some of them, recover that we are faced with the *post hoc propter hoc* dilemma. Is the result due to the remedy or to the *vis medicatrix naturae*? Until quite recent years that difficulty was principally met—when it was met at all—by comparing patients submitted to the new treatment with the patients the clinician had observed in past years. The problems of such a comparison were many. It was often not certain that the patients selected for the trial were comparable with those previously seen; those earlier patients were often not equally well documented, so that records were lacking and the comparisons necessarily crude; the numbers involved were frequently far too few to merit the confidence placed in them; and mortality from the same disease at different periods of time is affected by factors such as breeding out of highly susceptible stock, economic and social conditions, and variations in the infecting organism. With a new discovery that produces dramatic results there would rarely be any doubt about the answer, but such discoveries are rare. It is the smaller, yet often important, advances that it is difficult to substantiate—or disprove—by such rough-and-ready means. The meteoric rise and regrettably slower fall of many a form of treatment bear eloquent witness to the lack of the controlled trial in medicine. The application of such trials was gaining ground before the war and their value becoming more and more appreciated by the clinician—subject always, it must be stressed, to the fundamental ethical problem inherent in using human beings as the subject of experiment.

In developing the trial of streptomycin in the treatment of pulmonary tuberculosis, reported on page 769, the Medical Research Council's Committee was clearly relieved of this particular moral responsibility. It had allocated much of the limited streptomycin at its disposal to treating and observing two fatal forms of tuberculosis—the miliary and meningeal. It had, needless to say, a quite insufficient supply to treat all possible cases of pulmonary tuberculosis, and in this situation rightly set about planning a rigorously controlled investigation. The plan adopted is worthy of careful study in itself, quite apart from the results to which it led, for it may well serve as a model in this field.

To begin with, the Committee was clearly of a mind not to dissipate its energies—and its small supply of the drug

—in attempting to cover too wide or too ill-defined a field. It selected one type of case and defined it as rigidly as possible—acute progressive bilateral pulmonary tuberculosis of presumably recent origin, bacteriologically proved, unsuitable for collapse therapy, ages 15 to 30. In such trials it is often tempting to add little groups of patients of differing types here, there, and everywhere with the object of learning rather more. Though with a statistical design it will certainly sometimes pay to do so, very often the rather more becomes the rather less. Such a trial gives doubtful answers to the many points but no decisive answer to any. This temptation the Committee, and the clinicians co-operating with it, resisted.

Having defined the type of case it proposed to observe, the Committee next obtained the co-operation of various hospitals in carrying out the controlled trial and sought for suitable patients to place in their care. The important point here is that without some such central organization to direct the work, and without the collaboration of a number of hospitals in carrying it out, a sufficient number of patients of the same type will rarely be available. Small groups here and there will give conflicting answers. Then to ensure that the patient did conform to the features laid down the Committee set up a selection panel. This panel conceivably might have been influenced in selecting or rejecting a patient if it had known beforehand whether the patient was to be allocated to the streptomycin or to the controlled group—e.g., if alternate patients had been taken. It was relieved of any such worries by an ingenious system of sealed envelopes. Once a patient had been accepted an appropriate numbered envelope was opened, and not till then was the patient's group revealed. The allocation to "S" or "C" in this form had been made at random by the statistician. It is instructive also to see how close an equality of group characteristics this statistical method produced. For instance, 54% in the "S" group and 46% in the "C" group were in poor general condition at the start of the trial; 20 and 17 were desperately ill; 65% of "S" patients and 56% of "C" had a sedimentation rate over 50; 32 "S" and 30 "C" cases showed large or multiple cavities; in 19 of each group there was radiological evidence of segmental atelectasis. The random allocation has not only removed personal responsibility from the clinician and possible bias in his process of choosing patients, but has on the whole effectively equated the groups—fundamental, of course, to the general comparisons (the "S" group, as it happens, was slightly the poorer).

The hospitals to which these patients passed were provided beforehand with standard record forms designed specially for the trial, and examinations of the patient were required at fixed intervals. Thus uniform records were assured and any loss of essential particulars guarded against. Treatment was likewise standardized, though the clinicians in charge of the patients were naturally given freedom of action in urgent cases. To overcome any difficulties that might arise—indeed, were certain to arise in a trial of this nature—frequent meetings were held both of the clinicians and pathologists concerned, while the co-ordinator at the centre constantly visited the periphery. Clearly in this way much trouble was taken to ensure smooth running and to develop a co-ordination of methodology in every respect throughout the hospitals. Finally the monthly reports from the hospitals were assessed centrally, and thus again uniformly. In this assessment it may be noted that one of the fundamental criteria of the effect of the drug was bound to lie in the change in the radiological picture. To remove all possibility of bias the Committee had the films assessed independently by two radiologists and a clinician, each of whom had no knowledge whatever whether the film they saw related to a streptomycin or to a control case. Such a method vastly increases confidence in the results, and it is important to realize that it in no way questions the intellectual honesty of the investigator who is thus asked to work "blind." It guards not only against unconscious bias but, equally important, against any honest attempt in the assessor to allow for a possible bias.

It was by these careful means that the Committee reached its objectives—a rigorously controlled investigation, an impartial assessment of its results.

SOCIAL WELFARE AND VOLUNTARY ACTION

In his report on Social Insurance and Allied Services Sir William (now Lord) Beveridge told the Government of the day how the State could cure poverty by a comprehensive scheme of compulsory insurance. His new contribution to sociology[1] contains an account of the methods which have been used to alleviate misfortune. In effect he asks, Can the State, using all the means at its disposal, cure unhappiness? The answer is obviously No, even if we knew how to define happiness. A "good" society cannot be made without voluntary action for social advance even in what Lord Beveridge calls a Social Service State. He divides voluntary action into two categories, mutual aid and philanthropy. The best example of mutual aid is the friendly societies, which were established in order that men known to each other could pay money regularly into a common fund and draw on that fund when they were in need. But to the bulk of their 8,000,000 members in 1947 the friendly societies represented not good fellowship but a means of insurance by contract. In the first Beveridge report it was suggested that the friendly societies should be used as the agents of the Government for the distribution of State benefits to their members. Instead the marriage of 1911 between the State and the voluntary agencies has been followed by a divorce, and the State is now constructing a complete and exclusive administrative machine of its own.

Lord Beveridge gives some other examples of mutual aid societies, including the hospital contributory schemes, the growth of which he considers to have been one of the greatest successes of mutual aid in modern times. The need to provide for special expenses at death has been as widely felt as the need for security in sickness. From this grew the remarkable form of modern business known as industrial assurance. The Royal Commission which inquired into the work of friendly societies in 1871–4 did

[1] *Voluntary Action—A Report on Methods of Social Advance*, 1948. Allen and Unwin Ltd, London. Price 16s.

[2] "Report (1947) of the Committee on the Care and Treatment of the Elderly and Infirm." *British Medical Journal Supplement*, 1947, 1, 133.

not welcome this development, and it produced statistics to show that the insurance of young children's lives had led to increased mortality among the children insured. It therefore recommended that the insurance of the lives of children under 3 years of age should be prohibited altogether. When the national insurance scheme comes fully into operation it will be illegal to take out policies under which payments are made on the deaths of children under 10 years of age.

The philanthropic motive is defined as the desire by one's personal action to make life happier for others. The unobtrusive doing of good works is no longer a common occupation for the private individual. Certainly the basket of chicken broth and calves' foot jelly which, according to the Victorian novelists, the lady of the manor or the parson's wife took to the invalids in the village is a thing of the past. But, Lord Beveridge says, "democracy to-day has to show that in discarding the inequalities it can learn the virtues of aristocracy." There are fewer people than formerly with much leisure, but there are many more with a little leisure who might be willing to take part in some form of voluntary action. Among the more modern philanthropic organizations are the Nuffield Foundation and the King Edward Hospital Fund for London. How far organizations such as these have travelled from private charity can be judged by the fact that the income of the former for the year 1946–7 amounted to nearly £400,000.

The most difficult and perhaps the most rewarding of the problems which can be tackled by voluntary action is that of old age. It provides the best illustration of the needs which cannot be satisfied merely by providing a subsistence income. Old people should live in houses suitably planned for their needs; some require homes with service, and others, who are disabled by the diseases of old age, could enjoy life again if the "geriatric departments" suggested by the B.M.A. committee[2] were set up in selected hospitals. Determined efforts must also be made to prevent sickness among the old.

The unhappy child is a pathetic and appealing figure, and for many years there have been charities concerned with the care of orphans and deserted children. Readers of this book will probably learn with surprise that the N.S.P.C.C. had a hard struggle for recognition in its early days. The report of the Curtis Committee in 1946 showed that in spite of the efforts of charitable organizations and public assistance authorities the care of deprived children still left much to be desired. The field for voluntary action is wide, since deprived children include not only those without a home but also children who do not have a "normal" life at home because of the failings of their parents. Pity for the blind is widely felt, and there are at present 100 voluntary agencies looking after their welfare; they spend about £1,500,000 from private sources each year. The blind register kept by local welfare authorities, which shows where every blind person is who needs assistance, is the envy of blind-welfare organizations in other countries. There is no similar register of any other handicapped class in the community. The deaf do not receive the same statutory help as the blind, and Lord Beveridge describes the Government issue of free hearing-aids under the National Health Service Act as putting an end to the commercial exploitation of the widespread demand for devices to improve hearing.

Much help is now given to disabled persons in the way of training and sheltered employment, but the Disabled Persons (Employment) Act does not meet all their needs. The register which the Ministry of Labour maintains is incomplete—it is a register only of disabled persons who seek employment. Those who wrongly judge themselves incapable of any work will probably not register. Other classes of the community who can be helped by voluntary action are unmarried mothers and children, discharged prisoners, and last but not least the tired housewife. Lord Beveridge praises the Lancashire Council of Social Service for its pioneer work in establishing the Brentwood recuperative centre for mothers and children.

In discussing how the needs of the physically and mentally disabled can be met by voluntary action Lord Beveridge does not refer to the powers now given to local health authorities by Section 28 of the National Health Service Act (Prevention of Illness, Care, and After-care). These powers are very wide, and important developments in public health practice will certainly be made when the authorities learn how to use them. Already after-care committees are asking what sort of local help can and should be given to the physically and mentally disabled. The highly trained professional social worker such as the health visitor and the local resident who is prepared to give a little of his or her spare time should between them be able to remove some of the unhappiness which is felt by the old, the disabled, and the lonely.

One of the most significant conclusions drawn from a study of the problems brought to citizens' advice bureaux was that "the material cause of unhappiness, quarrelling, and perplexity in Britain, outweighing all others in importance, was lack of enough buildings in which to live, meet, teach, learn, and do all else that is meant by civilized life." A result of shorter working hours has been that the businesses of football pools, dog tracks, and other entertainments are all now exploiting in different ways the increased spare time of people not taught how to use leisure. Lord Beveridge believes that these are matters which can be put right by voluntary action, the ultimate aim of which should be to persuade the mass of the people that human society can be a friendly society.

"AS MAY BE REQUIRED BY HIM"

The local medical committee of the London Executive Council is to be congratulated on drawing attention to the slipshod wording of a paragraph of the model allocation scheme put forward by the Ministry of Health to executive councils for consideration. The ambiguity is explained in a letter printed in the *Supplement* at page 152. As Dr. Robinson says, the scheme provides that attendance at the patient's home shall be the duty of the practitioner "as may be required by him"—the patient. Clearly the duty to attend should depend on the patient's needs, not on his demands. No doubt an honest, if stupid, mistake has been made, but if local executive councils do not correct the phrasing in their allocation schemes, as London has already done, medical practitioners may be subjected to many unjustifiable summonses to patients' homes. Some executive councils outside London may have already altered

the wording of their schemes. If there are any that have not done so but have adopted the model scheme verbatim so far as this part of it is concerned, we would urge their medical members to take up the point in the interest not only of the profession but of the patients as well. The need for protecting practitioners from an abuse of their time is clear enough, but it is equally to the advantage of the sick that their medical attendants should be protected from the unnecessary demands of every crank and *malade imaginaire* who insists on the right to a visit in his home whenever he chooses to "require" it. The strain of medical practice is great enough without this added burden.

WHITE BILE AGAIN

The modern conception that infective hepatitis is a disease of the liver cells is based on apparently incontrovertible pathological evidence. Aspiration biopsies demonstrate the lesion for all to see, and serial examinations show the processes of healing or the progression to either atrophy of the liver or nodular cirrhosis. So complete and so satisfying is this picture that earlier theories are completely discarded. Nothing is heard nowadays about plugs of mucus blocking the biliary passages.

But just as contemporary opinion accepts the demonstrations of central lobular necrosis it should not be forgotten that earlier pathologists were equally satisfied by Virchow's mucus plug. Probably most practitioners can recall demonstrations of this which were convincing enough to them as students, though some may have become less enthusiastic when in their turn they were expected to demonstrate it. It is now realized that such plugs were not the cause of the jaundice but were the result of it; but in accepting this explanation there has perhaps been a tendency to disregard their presence and to forget the possibility that such plugs may sometimes cause symptoms.

Bergenfeldt[1] has recently published a paper which redirects attention to these matters. During an epidemic of infective hepatitis in Sweden he was asked to operate upon a patient who had been jaundiced for seven months and who was suspected of having a biliary obstruction. A nodular cirrhosis was found, and the bile ducts were apparently normal. During the operation cholangiography was performed, the contrast medium being injected directly into the common duct; a normal picture was obtained, there being free passage of the dye into the duodenum. To everyone's surprise this operation was followed by rapid clearing of the jaundice, and at operation for a ventral hernia two years later the liver was found to be macroscopically normal. Subsequently Bergenfeldt operated upon six other cases of hepatitis, irrigating the biliary tract with saline as well as performing cholangiography. If none of these cases was as sensational as the first—some had been jaundiced for only two weeks—each was followed by an equally prompt clearing of the jaundice and clinical recovery.

In order to explain these satisfactory results the author revives the conception that the biliary passages become blocked by desquamated cells and mucus. To support this theory he presents some post-mortem evidence and recalls the old method of treatment of prolonged jaundice by means of duodenal lavage with magnesium sulphate. This was a method which had a great popularity in France between the wars and was used by some in this country with occasional dramatic success. Cases of infective hepatitis in which the jaundice persists and deepens and in which considerable damage is done to the liver are distressing problems to the physician. Bergenfeldt's work gives hope that operative treatment may provide a means of affording relief. No less valuable, however, is his demonstration that apparently well-established cirrhosis can occasionally regress and complete recovery occur.

[1] *Acta chir. scand.*, 1947, **96**, 17.

THYROID ENLARGEMENT AND DRINKING-WATER

The Medical Research Council's War Memoranda provided a useful series of pamphlets summarizing available knowledge for practical purposes and reporting the results of specific investigations. They are sensibly going to be continued in peacetime, and the eighteenth (the first to omit "War" from the series title) has recently been issued.[1] The report is of an investigation of the relation between thyroid enlargement and the iodine and mineral contents of local drinking-water. The findings mainly concern school-children, of whom about 6,000 were examined, but some adults were also studied. The thyroid glands of the subjects were graded by eye as (1) invisible, (2) visible but soft, smooth, and symmetrical, (3) conspicuously enlarged without firmness, asymmetry, or nodular change, and (4) as pathological if enlargement was accompanied by the latter characteristics. This simple method enabled 80–100 children to be classified by two observers in an hour. Two observers are recommended "in order to provide a check in cases of doubt or difficulty." However, no data are given in the report regarding individual variation in grading, so that it is impossible to assess the reliability of the method.

The results broadly confirm the fact that the incidence of thyroid enlargement is inversely related to the iodine content of the drinking-water, but there are many discrepancies in detail. These are probably related to the hardness or softness of the water: where the water is very hard the incidence of enlarged glands is likely to be higher than in another area with water of the same iodine content but which is softer. That these suggestions are correct is borne out by selection from the large amount of data provided in the report, but it is odd in these days to find that not even the simplest statistical analyses have been applied to the figures to assess the significance of the conclusions.

Where a study was made of the state of the thyroid in all the inhabitants of a village in the goitrous region in North Oxfordshire the non-pathological enlargement was very differently distributed from the goitrous enlargement. The former was found in 35 and the latter in 114 of the 575 people examined. Of the enlarged glands 70% were present in the 16–26 age group, while the goitres were much more evenly distributed, most (23%) being in the 36–46 group. This may be taken to support the view that the enlargement is physiological in the sense that it reflects a greater need for thyroxine (and so for iodine) during puberty, and that it may not necessarily lead to goitre later. At the same time there is no doubt that this enlargement is a sign of iodine deficiency and calls for remedial action. Without entering into the question of what part the drinking-water bears in the total iodine intake, the widespread occurrence of thyroid enlargement found among the children warrants the practical recommendation of the investigators that the general use of iodized salt is desirable in Great Britain.

Mr. L. E. C. Norbury will deliver the Bradshaw Lecture before the Royal College of Surgeons of England (Lincoln's Inn Fields, London, W.C.) on Thursday, Nov. 11, at 5 p.m. His subject is "Proctology Throughout the Ages."

[1] Murray, M. M., Ryle, J. A., Simpson, B. W., and Wilson, D. C., "Thyroid Enlargement and Other Changes Related to the Mineral Content of Drinking Water (with a Note on Goitre Prophylaxis)," *Medical Research Council Memorandum No.* 18, 1948. London: H.M.S.O. Price 9d.

SOUTH AFRICAN MEDICAL CONGRESS

MEETING AT PRETORIA OVERSHADOWED BY TRANSVAAL DISPUTE

The 36th South African Congress was held this year at Pretoria. A very successful meeting on its scientific and social side, it took place in the midst of the struggle over the Public Hospitals Ordinance in the Transvaal, which was due to come into operation within a week of the opening of the Congress and which has aroused the almost unanimous opposition of the medical profession in the Province. The annual general meeting of the Federal Council of the Medical Association of South Africa which preceded the Congress was largely occupied with this controversy.

At the official opening of the Congress in the City Hall Dr. C. G. L. van Dyk was formally inducted into the presidential chair by Dr. A. W. S. Sichel, president of the Federal Council. In his address Dr. van Dyk quoted the favourable health statistics of Pretoria, and went on to discuss the question of pain and its manifestations among the different races of South Africa. Field-Marshal Smuts addressed the assembly on communal health and nutrition and spoke of the importance of research in this field and the need for financing health measures by the modern State. On behalf of the Royal Society of Medicine in London its emissary, Mr. L. R. Broster, presented the Field-Marshal with the roll of honorary fellowship of that Society, together with a specially bound edition of the reports which the Society has published of the Inter-Allied Medical Conferences held under its auspices during the war.

The first plenary session of the Congress was devoted to the subject of malignant disease. Dr. F. J. Murray discussed the question of carcinogens in the production of neoplasms and the physical and biochemical changes found in cells. Professor M. Cole-Rous outlined a comprehensive scheme for tackling cancer by educating the public, training the general practitioner, co-operation between surgeons and other specialists, and better facilities for detection and research. Dr. M. Weinbren spoke of the types of carcinoma to be treated by surgery and radiotherapy, and suggested that expectations about radioactive isotopes had not been fulfilled. Dr. M. Suzman reviewed the part played by the endocrines in the production and treatment of cancer.

At another plenary session the subject of discussion was arthritis, and was introduced by Professor G. A. Elliott, who thought that the advance of medical treatment had been hindered by an uncritical approach. Other speakers dealt with clinical types, the plethora of treatments, and the role of physical medicine in the management of the condition. The economic and social aspect was also considered. Many sectional meetings were held. One combined meeting of certain sections was addressed by Mr. Broster on the adrenal cortex and the effect of adrenalectomy on steroid metabolism. Other sectional subjects were bone syphilis in the African native, peptic ulcer, contact dermatitis in certain trades, health education, and social medicine.

The Hospital Plan in the Transvaal

The Transvaal Administration Ordinance enacts free hospital treatment for all members of the community (including the 30% or so of Europeans, who have hitherto paid their hospital charges and doctors' fees) and the setting up of medical centres. A plebiscite of the profession in the Transvaal showed a majority of well over 90% against the ordinance. The effect of the provision and the grounds of the medical opposition were described in the *Supplement* of Sept. 18 (p. 123).

The Administrator has refused to consider a means test, which is not indeed provided for in the ordinance itself. A motion from the Southern Transvaal Branch, afterwards adopted by the Federal Council with one exception, was that members of the Association should be advised not to enter the Provincial Health Service. While the Congress was proceeding at the end of July an arrangement was agreed to whereby, pending a review of the situation by the Transvaal Provincial Council, members of the profession would continue their services in the hospitals after the appointed day (Aug. 1) on a voluntary basis.

Unfortunately, in these resumed negotiations, no solution has been found, and in an attempt to break the deadlock the Provincial Administration by-passed the Medical Association and made a personal approach to every doctor on the honorary staffs of provincial hospitals, asking him whether he was willing to carry on and what remuneration he would require. The first of four questions addressed to members of the staff of the Johannesburg General Hospital was as follows:

"Are you prepared to continue in attendance on the patients in hospital under your care as at Sept. 30 until they are discharged by you? If so, do you wish to continue such attendance on an honorary basis, or on a basis of receiving payment by the Administration; if the latter, what would you consider reasonable remuneration?"

The Medical Association thereupon advised its members to refuse to negotiate directly with the Administration, and stated that if they complied with the request concerning remuneration they would render themselves liable to disciplinary action on the ground of "tendering." The response to the Association's advice is given in the words of Mr. H. F. Prentz, chairman of the Hospitals Advisory Committee and one of the advocates of the Administration's scheme: "With few exceptions, the instructions of the Association have been obeyed. This is a very creditable display of loyalty and solidarity—on the face of it." But he added that it was reported that what amounted to threats of victimization had been used to prevent members from accepting posts under the new ordinance. These allegations have been indignantly denied. A spokesman of the Federal Council described them as "despicable." He said that the doctors were actuated only by a desire to prevent interference with their livelihood; there was no wish to wreck the ordinance, and the medical profession would see to it that medical teaching continued and that the sick poor and emergency cases in hospitals were treated despite the impasse.

The latest advices are that the South African Medical and Dental Council, which controls and directs the profession in the Union under powers given by the Medical Act, is taking up the question directly with the Union Government, considering that the breakdown of clinical medical education constitutes a national emergency, because the doctors who refuse to fill the posts offered by the Province would automatically be the teachers under the scheme. Moreover, it would be impossible for the hospitals in the Transvaal to carry on their medical services, because the full-time staffs are inadequate in the big hospitals and non-existent in the smaller.

BRITISH ASSOCIATION OF PLASTIC SURGEONS

CLINICAL CONGRESS

The British Association of Plastic Surgeons, which was formed in November, 1946, held its Summer Congress on Sept. 16, 17, and 18 at Oxford and Stoke Mandeville under the presidency of Professor T. P. Kilner. The meeting was attended by 90 delegates, including members and visitors from America, Belgium, Denmark, Ireland, Norway, Sweden, and South America.

Dr. Sumner L. Koch (Chicago), the guest of honour, addressed the Association on the surgery of the hand. He had found that healing had been more certain since the application of antiseptics had been abandoned. Ordinary soft white soap was used to prepare the operative field the afternoon before the operation and again, by an assistant, on the operating table. He used an inflatable arm-cuff, and was prepared to leave this on for as long as three and a half hours as a tourniquet during the operation. No sign of paralysis has yet been seen using this technique. The cuff was deflated at the end of the operation to allow the ligation of any large vessels, and was then reinflated until the final bandage had been applied.

Dr. Koch said he would not suture tendons divided within the digital sheath, since the blood supply was so poor, but preferred to use a tendon from the dorsum of the foot as a graft, passing this around the base of the distal phalanx. All suturing was carried out with fine silk in preference to any form of wire; he had had no personal experience of wire, but had not been impressed with the results where it had been employed. Tendon grafts to fingers were never undertaken until all the joints were mobile. For uniting divided nerves he advised the finest cataract silk on eyeless needles in the form

of simple interrupted sutures. The hand and fingers were splinted in full flexion for three weeks, and this was followed by splinting to prevent full extension. The results of nerve suture were very poor if it was carried out more than two years after injury. Finally Dr. Koch demonstrated a simple ball-and-gutter type splint which was used to maintain the hand in the position of function and could be applied to either hand.

The second day of the Congress was spent at Stoke Mandeville, where papers were presented during the morning by members of the Plastic Surgery Unit. Mr. R. J. V. Battle, discussing the treatment of decubitus ulcers in paraplegic patients, emphasized that free grafts were of no value. Carefully planned local flaps were the solution to this problem, but operations should not be undertaken unless the patient was in good condition, for, at best, healing tended to be delayed.

Mr. R. P. Osborne, discussing facial paralysis, said that these cases should be sent to the plastic surgeon very much earlier than was the custom. Many of the poor results following recovery of nerve function, or after a nerve-grafting procedure, were due to stretching of the paralysed muscles in the intervening period.

Professor T. P. Kilner projected a number of slides illustrating the commoner secondary cleft-lip and palate deformities and the results of their treatment. Other papers were on haemangiomata, by Mr. J. P. Reidy; oro-antral fistulae, by Mr. E. W. Peet; mandibular asymmetry, by Mr. D. Greer Walker; and the use of prefabricated cartilage inlays for pinna support, by Mr. H. E. Blake. During the afternoon a ward was set aside for the demonstration and discussion of selected cases. The lecture hall was transformed into a projection-room for a continuous show of films from the Stoke Mandeville Plastic Unit library, and the dental department arranged a demonstration of the extensive work they have done in association with the Plastic Unit. Dinner was held in the Hall of St. John's College, and the evening concluded with interesting and informal talks by W. C. Costin and H. W. Thompson.

The morning of the last day was occupied by the presentation of papers by visitors from America: Dr. Gustave Aufricht (New York) on mammaplasty; Dr. Milton Adams (Memphis) on an operation for bilateral hypertrophy of the masseter muscle; and Dr. Neal Owens (New Orleans) on osteoporosis following burns. During the discussion on mammaplasty both Professor Kilner and Sir Harold Gillies emphasized that reliance should not be placed entirely on the skin to provide the shape of the breast.

MEDICAL MICROFILM UNIT

The microfilm unit of the Royal Society of Medicine has been installed in reconstructed (formerly bomb-damaged) premises in Dering Yard, New Bond Street, close to the Society's headquarters, and was formally opened on Oct. 18. Hitherto the unit has worked in cramped quarters at the Society's house, but now it occupies three floors of one building and has printing, developing, and drying facilities, so that it is possible to turn out 25,000 pages of microfilm a day. The unit was opened by the Chief of the Scientific Mission at the U.S. Embassy, Dr. Earl A. Evans, who at the last moment took the place of the American Ambassador, and representatives were present from the Foreign Office, the Ministry of Health, the Ministry of Works, the Medical Research Council, the British Council, Unesco, and the Centre Nationale de la Recherche Scientifique of Paris.

Sir Henry Dale, President of the Royal Society of Medicine, in calling upon Dr. Evans to unveil a tablet commemorating the occasion, stated that the creation of this unit for the production and distribution of microfilm copies of medical publications covering many countries had been made possible by the munificence of the Rockefeller Foundation. For many years the Royal Society of Medicine had been developing the service of its medical library not only by lending its books to its members but by preparing bibliographies for them and making photostat copies of articles or extracts on request. Such a service became increasingly difficult to maintain when war broke out and the medical men who needed these facilities were scattered all over the world, but the invention of the microfilm made it possible to continue the supply of material, a camera in the Society's house being used for the purpose, and the films, with the necessary projectors for reading them, being conveyed to their destinations from the Rhine to the Jumna by the R.A.F. As the war progressed, however, it was realized that there was here an opportunity for a larger service owing to the appalling devastation of libraries whereby much of Europe and even of Asia was becoming largely bereft of these sources of medical and scientific knowledge.

Much encouragement was given by the Minister of Health, who helped the Society to secure the necessary licences for rebuilding and equipping the premises, and ensured the good will of his colleagues in the Foreign Office and Board of Trade. Sir Henry Dale said that if Mr. Bevan "was not already surfeited with expressions of gratitude from medical quarters" they would like to convey to him an expression of their thanks for the support he had given to this enterprise. A well-equipped unit was now available with an efficient staff. The first objective was to restore the war-damaged libraries of Europe and beyond by means of microfilm copies of medical journals which they had lost and which were out of print or otherwise irreplaceable. The majority of medical libraries, to the total number of 173, were associated with the scheme, which ranged from Reykjavik to Singapore, and 3,500 volumes otherwise unobtainable had already been supplied, and there were orders for at least 10,000 more.

Dr. Earl Evans, in performing the opening ceremony, spoke of America and Great Britain as sharing a common medical tradition, and said with what gratification the United States, in the shape of the Rockefeller Foundation, found itself associated with this project. Scientific progress was only possible where research was unhampered, as it was in their respective countries, and where free interchange took place.

MEDICAL FILMS

In connexion with the second International Congress of the Scientific Film Association, recently held in London, a "Film Festival" was arranged during which the applications of the film to education, medicine, and industry were demonstrated. Some two dozen films were shown, varying in length from three to thirty minutes. Most of the films were intended for medical education and research, but a few were designed for health propaganda to the cinema-going public. Some of the films had been produced in medical schools. One of them, summarizing the first clinical lecture to medical students on the subject of acute inflammation, was the work of the department of medical photography at Westminster Hospital Medical School, and another, illustrating a case of chorea, the work of the department of child health at Guy's Hospital. Others were the production of individual workers—for example, Mr. Gwynne-Evans's ingenious 20-minute reel showing the behaviour of the oro-facial musculature during breathing and swallowing, Dr. Bryan Stanford's short films on how to evert the upper eyelid and how to apply the Aschheim-Zondek test for pregnancy, and Dr. David Morris's excellent clinical case record of hereditary ataxia. Other films came from the great commercial film houses or the laboratories of food and drug manufacturers, and yet others from American and Continental universities, the State Film Centre at Copenhagen, and the National Film Board of Canada.

This heterogeneous collection was unequal in value, and the more elaborate films were not necessarily the best. For example, one film from Denmark which showed the systematic examination of a patient for signs of syphilis, while it indicated the technique for examining skin, mucous membranes, and lymph glands, was criticized on the ground that it gave no indication of the lesions which were discovered. A film from New York University which was described as an integrated study of the interaction of the child with his environment showed the behaviour of small children and their parents at a psychiatric interview, but no allowance appeared to have been made for the probability that the presence of the camera had a disturbing effect on the parents in handling the children, even if the children themselves were too young to be influenced by its presence. On the other hand, some of the short films were admirable for teaching purposes and clinical records, as, for example, the work of the Wellcome Film Unit in illustrating

cases of rheumatic chorea and myasthenia gravis, or of the Research Unit at Columbia University illustrating the toxic effects of streptomycin, particularly on the eighth nerve.

The medical film is no longer a novelty, and those attending the demonstrations were reminded of what has been achieved in the course of a quarter of a century. In connexion with the recent centenary of the American Medical Association a film was prepared showing the evolution of the medical film itself. A copy was kindly sent to the British Medical Association, which allowed a private preview on this occasion. "The Medical Film" is a 16-mm. reel, running for 25 minutes. It is in colour and is accompanied by a sound commentary. It reviews the development of the medical film since the early 'twenties—the introduction of the animated cartoon, the combination of the film with radiography and with photomicrography, and the progress in colour. It is put together with the usual American talent for production. A sight of the early films of operations made one wonder how anyone could have learned anything from those confused moving masses of black and white. A British film of the operation of subtotal hysterectomy for multiple fibromyomata followed. It was recorded for post-graduate teaching and exemplified the high level of cinematic technique now attained.

Subcommittees have been set up to study the following problems: "(1) The establishment of an international data card for compiling a master index of scientific films available throughout the world and the formulation of methods of appraisal of these films. (2) The joint production by a number of countries of films of common interest. (3) The exchange and distribution on the widest scale of scientific films and the customs regulations affecting such exchange. (4) The setting up of a scientific-film reference library. (5) The exchange of information between nations by means of a regular journal."

SCOTTISH SOCIETY OF THE HISTORY OF MEDICINE

The third meeting of the Society was held in the Hall of the Royal Faculty of Physicians and Surgeons, Glasgow, on Oct. 20, with Dr. Douglas Guthrie in the chair. Professor J. D. Mackie of the chair of Scottish history and literature, University of Glasgow, described how the early history of Glasgow was dominated by that of the bishopric of the city. The University, founded in 1451, was at first modelled on French lines, but after the Reformation it was reorganized by Andrew Melville, and since then it had taken its place as one of the great seats of learning in the world.

Mr. A. L. Goodall, honorary librarian, said that the Faculty was unique among medical corporations in this country in that both physicians and surgeons were united in one body. The Faculty, founded in 1599 by Maister Peter Lowe, received its charter from James VI the same year. Among its many duties were the examination and licensing of all surgeons in the West of Scotland, supervision of their conduct, and ensurance that any drugs supplied were of the highest quality. A service of free medical aid to the poor of the city was a noteworthy feature of the Faculty's activities. Many famous men in medicine and surgery, like Cullen, Lister, and Macewen, had associations with the Faculty, which will celebrate next year its 350th anniversary.

The Ministry of Health states that full-time nursing and midwifery staffs in hospitals in England and Wales now part of the National Health Service have risen by 2,000 within 12 months. In June last the total, including those trained and in training, was 117,741, compared with 115,529 a year earlier. Part-time nursing and midwifery hospital staffs over the same period rose by nearly 7,000—from 10,700 to 17,380. On the domestic side full-time staff went up from about 96,500 in June, 1947, to 99,700 in June, 1948, and part-time from 18,000 to 21,575. This general increase in hospital staffing has not only made it possible to shorten the nurses' hours in many hospitals and to institute a 96-hour fortnight but to reopen beds closed through lack of staff. In mid-1947 there were about 63,000 beds out of action for this reason, but by June this year nearly 6,000 of them were again available for patients. Every addition to the hospital nursing and midwifery staffs now means either the opening of more beds or the improvement of working hours and conditions, and sometimes both.

Correspondence

Neonatal Asphyxia

SIR,—While all must admire the way in which Dr. F. C. Eve (Sept. 18, p. 554) insists on the mechanics of resuscitation, it does seem sad that he and nearly everyone else should ignore the brilliant researches of the late Sir Joseph Barcroft into the physiology of neonatal respiration. He showed quite conclusively how minute was the amount of oxygen in the foetal circulation at birth and how the agent in starting respiration is not oxygen lack or carbon-dioxide stimulation but sensory stimuli either from the skin or from muscles or other organs. The foetus that does not breathe may be suffering from a type of shock, but it is fundamentally a different type from surgical shock. What it awaits is some stimulus which will penetrate to the brain and cause the reflex respiratory efforts which nature has provided for.

I have drawn attention in previous letters to the way in which Barcroft's researches entirely explain the dramatic way in which an injection of "cardiazol"-ephedrine starts an asphyxiated foetus into full respiration in a matter of seconds, but this fact is consistently ignored in all the textbooks of midwifery that I was able to see at the B.M.A. exhibition at Cambridge this year. The latest one, a pre-publication copy I saw last week in London, even speaks of "sadistic attacks" on asphyxiated babies, as if Freudian jargon could replace or displace exact scientific knowledge. If the author had listened to the late Sir Joseph he would have learned that the nose of the foetal sheep is the area which first shows any response to stimulation, and it is on this area that the lamb normally falls when it is dropped, thus providing the maximum stimulus on the most sensitive area in order to ensure the immediate commencement of respiration. One might think that the spirit that refused to listen to Semmelweis still stalks in our maternity wards, for asphyxia, which directly or indirectly causes 75% of neonatal deaths as well as many more still-births, is still treated as if one of our greatest experimental physiologists had never shown a better way. And not only do babies die but homes are plunged in grief (as I know, for my first child was still-born) because doctors will not apply the very simple and effective remedies that science has provided to make use of the knowledge that has been gained.

Dr. Eve rightly touches on the question of the final result of these long-asphyxiated babies. The first baby I saw that was so long asphyxiated that I ventured to give it cardiazol-ephedrine intracardially, now nearly 9 years old, has never needed any medical attention and is very bright mentally, and all the others are normal. I quoted my last case recently in the *Practitioner*, and, though one swallow does not make a summer, this one case does mean that we must radically alter some of our conceptions of neonatal asphyxia. It was a child born with a fairly easy forceps delivery that breathed promptly and well. In 15 minutes or so the breathing began to get weaker and gradually ceased entirely, the child becoming blue and finally white. Before he reached this stage I had given him first 0.5 ml. of cardiazol-ephedrine intramuscularly and then a second dose, without any appreciable effect. When he seemed quite dead I gave him yet a third dose into the left ventricle, and this, to my amazement, was followed by an almost instantaneous resumption of respiration and crying. I was no less surprised when the babe was living next day, and now he is a bonny babe of 7½ months, already beginning to say "Baba, Dada," etc.

I think that practically every doctor would have said without hesitation that this was a case of fatal intracranial injury, yet it was apparently merely a case in which for some reason the brain did not sufficiently well change over from its initial response to sensory stimuli to regulation by oxygen and CO_2 in the blood. If this is true, it is of the utmost importance that we should recognize that such a failure can occur, for looking back I can now recall several cases in which this may well have been the cause of neonatal death, and the case I have quoted suggests that appropriate treatment might have

prevented it. There is little doubt that such treatment would also avoid the later complications of feeble initial respiration —i.e., pneumonia, etc.

I may perhaps also recall a case I reported in 1940, a boy drowned from long immersion who recovered rapidly after treatment based on the assumption that this basic pattern of respiratory response to cutaneous stimuli persists, as at birth, after the response to carbon dioxide has been lost through poisoning of the respiratory centre. The bearing of this supposition on the treatment of anaesthetic as well as drowning casualties is obvious. These are all problems of applied physiology, and I suggest that it is not to the credit of British medicine that in this country, where the key was found, they have been so long and so disastrously ignored by those whose work the discovery would most benefit.—I am, etc.,

Winsford, Cheshire. W. N. LEAK.

Ruptured Uterus

SIR,—I am in agreement with Mr. C. Scott Russell (Oct. 16, p. 722) in his condemnation of classical caesarean section. It is an operation practised all too commonly in this country. I would go further and suggest that in abdominal hysterotomy, with or without sterilization, it is possible to perform a lower-segment operation but in miniature. The uterus can be incised transversely above the internal os and the peritoneum of the utero-vesical pouch used to cover the incision.

Recently I saw a case of rupture of the uterus at term which followed an abdominal hysterotomy for placenta praevia at the 24th week of a first pregnancy. The rupture of the uterus extended from fundus to cervix as in Mr. Keith Vartan's case (Sept. 25, p. 602). It was possible to conserve the uterus, and the woman has since menstruated normally. The transverse fundal incision for abdominal hysterotomy carries with it not only the danger of rupture but also intestinal obstruction.—I am, etc.,

London, W.C.1. W. C. W. NIXON.

Classical Caesarean Section

SIR,—Mr. C. Scott Russell (Oct. 16, p. 722) surely uses rather harsh words when he condemns as an "abomination" an operation (classical caesarean section) which has saved countless foetal and maternal lives. Though the classical caesarean section is admittedly not an edifying spectacle and has certain disadvantages, including occasional rupture of the scar subsequently, one can recall so many classical operations in the past that have had a happy outcome both at the time and in subsequent pregnancies. Lest one be carried away by a youthful enthusiasm for the lower-segment operation to the exclusion of any other it might be well to remember that there are still certain cases in which the classical operation is probably safer.

The type of case I have in mind is that in which, on opening the abdomen, one sees an enormously rich venous plexus overlying the lower segment, sometimes associated with placenta praevia. I have often in such cases retracted or enlarged the abdominal incision upwards and performed the "abominable" operation with a sigh of relief. It is better, I think, provided it is a "clean" case, to accept the relatively slight and more remote risk of subsequent rupture of the scar than the immediate one of severe bleeding. Surely this is an example of where one must adapt the operation to the patient, not the patient to the operation.—I am, etc.,

Exeter. P. M. G. RUSSELL.

SIR,—Mr. Keith Vartan's medical memorandum on "Ruptured Uterus" (Sept. 25, p. 602) has reopened the caesarean controversy, and I am interested to see the fervour with which Mr. C. Scott Russell (Oct. 16, p. 722) condemns the classical operation. He follows the fashion of the moment which condemns the older operation out of hand. Other operations have suffered the same unthinking treatment and have subsequently been received back into favour by a later generation which has found out advantages which their fathers were too blind to see.

The lower-segment operation has such obvious advantages in most circumstances, for reasons which are too well known to repeat here, that it is rightly used in the great majority of cases. But there will always remain a small number of young women in whom an elective section is necessary and in whom there is good reason to expect a normal delivery in a future pregnancy. It is very necessary that the form of operation performed in such patients should not prejudice this possibility, and I have the idea, backed by a reasonable amount of personal experience, that the transverse scar of the lower-segment operation interferes by its interruption of the neuromuscular pathways both with the proper relaxation of the cervix and with the reflex from pressure on the latter which helps to maintain the pains of labour. I have often been disappointed in the progress of labour in women who have had a previous lower-segment operation, even to the point of having to perform a further section for no other reason than mere lack of progress after many hours of poor pains in the absence of any other complicating factor. On the other hand, it is the usual experience that in similar circumstances the woman who has a classical scar has a quick and easy labour. Some will counter this by saying that the incision in the lower segment should be longitudinal; but if a woman is only in the early stages or not in labour at all an up-and-down incision becomes a lowly placed classical one—and this is the right position for a classical scar anyhow.

I seldom perform the classical operation myself, but I am sure that this complete condemnation of it is illogical. From the physiological aspect the transverse incision is wrong, but we accept it in most cases because there are other more important reasons for doing so. But there is no reason to persist when none of these reasons is present and there is a strong desire to preserve a fully physiological organ. I do not believe that a lowly placed classical scar—that is, one which follows an incision which is started as low as possible in what there may be of a lower segment at the time and is continued upwards only as far as may be necessary—is more likely to rupture than one wholly in the lower segment in whatever direction it may run.

Until more is known about it I shall continue to avoid cutting across the uterus for this reason and shall be content to make my incision in the up-and-down direction in the few suitable cases, even if this means that I must occasionally trespass into the forbidden upper segment. My lower-segment operating record will be sullied, but I shall have, I believe, done the lesser evil, and perhaps I shall be doing fewer repeat performances.—I am, etc.,

Swindon. GUY ROWORTH.

Post-gastrectomy Syndrome

SIR,—In the annotation on the post-gastrectomy syndrome (Sept. 11, p. 524) the following statement is made: "This conception is of particular interest in view of the similar syndrome which is known to follow vagotomy for duodenal ulcer, and careful observation of these cases is indicated."

I feel that this statement may arise from a misunderstanding, for I have not observed a single example of such a syndrome during the follow-up of seventy cases of vagal section, nor have I seen a single reference in the literature to it (as an abstracter I have access to most of the literature on the subject). Reference to the text of the article by Dr. W. T. Irvine (Sept. 11, p. 514) on which your annotation was based lends support to this view, for your meaning could be read into one sentence taken out of context: "Moore *et al.* (1947) also observed such post-prandial symptoms following vagotomy."

In its context the meaning of that sentence is that most gastric sensations, as for example a feeling of distension, could still be appreciated after vagotomy. The observation was made to support the thesis that sensation is not carried in the vagal nerves. In Moore's[1] article the relevant passage is: "Nausea, vomiting, and epigastric sensations of fulness may still be experienced." But this does not indicate that they are experienced as a syndrome, as can be seen from the sense of the rest of that sentence, ". . . and there is no change in the sensory threshold to balloon distension of the oesophagus, stomach, duodenum, jejunum, and ileum."

I would be grateful if you would clarify the point by publishing the reference to the work in which the report of a "post-gastrectomy-like" syndrome in vagotomy cases is made. If it is a fact that it has occurred, then, as you state, it is important enough to warrant careful observation of

vagotomy cases, for in those cases the autonomic balance has been upset in favour of the sympathetic. Unfortunately no good evidence has been provided in the post-gastrectomy cases that adrenaline secretion can be blamed for the symptoms; it would have been of some assistance if blood pressure recordings had been made.

Finally, it would be interesting to know what proportion of Dr. Irvine's series of gastrectomies these 24 cases provide.—I am, etc.,

Birmingham. B. N. BROOKE.

REFERENCE

1 *J. Amer. med. Ass.*, 1947, **133**, 741.

*** H. D. Johnson (*Proc. R. Soc. Med.*, 1948, **41**, 649) reported that about one-third of his patients had attacks of weakness, sweating, and faintness after vagotomy and that two patients investigated had hypoglycaemia during an attack.—ED., *B.M.J.*

Diabetic Coma

SIR,—Professor E. P. Joslin (Oct. 2, p. 657) makes a request for constructive criticism. Impressed by his series of 62 consecutive patients with diabetic coma without a death, at the beginning of 1944 we issued to medical staff, ward sisters, and students at the Radcliffe Infirmary a summary of the treatment suggested in the paper by Joslin, Root, White, and Marble in the *Journal of the American Medical Association* (1942, **119**, 1160). The death rate from diabetic coma since this change has been reduced to about a third of its previous level.

My first patient treated on the Joslin regime was a young woman in deep coma with previously undiagnosed and untreated diabetes. She made what we thought was a good recovery. On the following day she asked the nurse for a drink, and on being sat up to receive it fell back dead. The post-mortem examination revealed no gross organic disease. We therefore added to our summary of treatment a paragraph as follows:

"*Aftercare.* It is important to realize that a patient who has come round from diabetic coma has recently been in a condition of profound circulatory failure and is still ill. The patient should not be allowed to sit up in bed, and should be nursed as a cardiac case for at least a week."—I am, etc.,

Oxford. ALEXANDER COOKE.

The Walking-calliper

SIR,—Dr. H. L. Rogerson (Oct. 16, p. 724) writes that he does not know of an organization concerned with research in this particular instrument (the calliper). In 1945 the British Orthopaedic Association appointed a Surgical Appliances Subcommittee to investigate the design, materials, and manufacture of surgical appliances and the calliper in particular. The personnel of this Committee includes an anatomist, a physiologist, an engineer, the director of a large appliance factory attached to an orthopaedic hospital, as well as orthopaedic surgeons. The Nuffield Provincial Hospitals Trust has generously supported the research, so that it was possible to appoint an engineer as a Research Fellow.

The problem of the calliper has taken precedence in the investigations, which are not yet completed. The important matter of standardization of small parts and screws, so that repairs can be carried out without delay, is one item of policy stressed by the committee.—I am, etc.,

ST. J. D. BUXTON,
Chairman, Surgical Appliances Subcommittee, B.O.A.

London, W.C.2.

Bronchial Carcinoma

SIR,—Mr. R. C. Brock in his paper on bronchial carcinoma (Oct. 23, p. 737) remarks that though there remains much room for improvement in the surgeon's technique in dealing with this condition "the greater responsibility rests with those who have the task of making the diagnosis or thinking of the diagnosis." With this dictum I am in general agreement; but I would suggest that there is at present an even more disheartening obstacle to the efficient application of surgical measures than diagnostic delay. This is the difficulty and delay experienced in the admission of patients to hospital. Even when the diagnosis has been established and the case is regarded by the surgeon as suitable for an attempt at radical treatment it is often a matter of the greatest difficulty to find a bed in a thoracic surgical centre.

I do not wish to discuss controversial aspects of this problem such as the present deplorable necessity to assess priorities to be given to various categories of patients—for instance, to young patients with relatively curable conditions such as unilobar bronchiectasis or pulmonary tuberculosis requiring surgical treatment relatively to older patients with malignant disease whose prognosis even with surgical treatment is on the whole unfavourable. My object is to stress that, as long as there is delay in securing admission of a patient with possibly operable bronchial carcinoma to a suitable centre for surgical treatment, responsibility for failure to make generally available the benefits of advances in surgical technique rests with those responsible for the organization and administration of our hospital services even more than with the clinicians responsible for making the diagnosis.—I am, etc.,

London, S.W.3. J. G. SCADDING.

Reactions to Intravenous Sclerotics

SIR,—Though most would agree with Dr. R. E. Sidebotham (Oct. 2, p. 661) that sodium morrhuate is an obsolete drug—the Council of Pharmacy and Chemistry of the A.M.A. in 1942 recommended the withdrawal of the 10% solution—I think it would be unfortunate if the impression were produced that monoethanolamine oleate is entirely free from risk.

In the course of the past year, during which I gave about 1,000 injections of "ethamolin," two serious reactions were encountered. A severe urticaria developed ten days after one injection, but the other case was more alarming. Like Dr. C. E. Taylor's case (Sept. 18, p. 573), the patient had left the hospital, when she became faint. She was brought back by a passer-by and, when I saw her some twenty minutes after the injection, appeared moribund. Rapid deterioration was followed by a slight convulsion and apparent death. Fifteen minims (0.9 ml.) of 1 in 1,000 adrenaline was given intramuscularly, and almost simultaneously the colour improved and she began to breathe. Consciousness gradually returned, but about ten minutes later severe asthma developed. This responded to 7 minims (0.42 ml.) of adrenaline, but was followed by two further attacks at ten-minute intervals also responding to 7 minims of adrenaline.

The patient remains well since; she has never had any other attacks of asthma or evidence of allergy. The injection which produced the attack was the sixth given into residual varicosities after a ligation and injection operation. The previous injections had produced no unusual effects. As a result of this alarming experience I would stress that whatever agent be used patients should be asked to wait a short while after their injection, and, of course, adrenaline should always be available.—I am, etc.,

Shrewsbury. J. A. RUSSELL JOHNSON.

Maxillary and Mandibular Neuralgia

SIR,—In his reference to Costen's syndrome as a cause of facial neuralgia Dr. J. H. Young (Oct. 2, p. 660) mentions pain which may be unilateral or bilateral, local, or referred to jaws, eye, ear, or mastoid; but he does not mention the grating, clicking, and locking of the joint with the restriction of movement which are very common features of traumatic temporomandibular arthritis. If the condition is unilateral there will be a swing of the jaw to the affected side on opening the mouth. A burning sensation in the tongue, glossodynia, and even tinnitus and deafness are also described as part of the syndrome, though they are not so common as the pain, grating, and limitation of movement which are usually the prominent features in traumatic arthritis.

I am writing particularly, however, to point out that this condition is in my experience not confined to edentulous patients, but is even more common in patients who have still got many of their natural teeth but who suffer from "close bite" either acquired through extraction of the back teeth or appearing as a result of developmental irregularity in the arrangement of the teeth. These patients have in the first case lost their molar support, and in any case have no free

lateral movement of the mandible owing to the interlocking "bite." Both of these conditions throw an extra strain on the articulation, setting up the arthritis, which the patient often aggravates by constantly fidgeting and moving the joint when it should be at rest.

It is rare to see any radiographic change in the joint, and such patients may be much relieved by wearing a shield affair over the biting surface of the upper teeth and palate which opens the bite and gives freedom to lateral excursions of the mandible. They may, however, be unwilling to give up wearing the shield even when cured, and if they are pressed to do so may get a recurrence of the neuralgia.—I am, etc.,

London, W.1. E. WILFRED FISH.

A Sign of Pregnancy

SIR,—I have recently encountered for the third time in the past five years a clinical sign which I have failed to find described in the text-books of obstetrics. This is a modification of the well-known Hegar's sign of pregnancy—namely, softening and compressibility of the lower uterine segment which is characteristically present about the 8th to the 10th week.

This same softening and compressibility of the lower segment is probably responsible for an undue lateral mobility of the body of the uterus, so that on bimanual examination one finds a swelling apparently located in one or other uterine appendage which, as in the commoner Hegar's sign, appears to be quite separate from the cervix. The body of the uterus cannot of course be felt separate from this swelling, but it may well give rise to confusion and suggest the possibility either of an ovarian cyst associated with pregnancy, as in a case referred to me last week, or possibly of a tubal pregnancy, especially in a nervous primigravida whose abdominal musculature is poorly relaxed on examination. Under anaesthesia examination will reveal the true state of affairs, and by gentle manipulation the swelling can be made to occupy the corresponding position in the opposite side of the pelvis, but it should often be possible to recognize the condition even without anaesthesia.

I am prompted to write this letter for the purpose of placing this sign on record since I feel that it is of some importance. I have been unable to find it described in any of the textbooks available to me, and I should be glad to know whether it has in fact been previously described and also whether other obstetricians have observed it with any frequency.—I am, etc.,

Inverness. J. A. CHALMERS.

Shipping the Sick

SIR,—As a ship surgeon of over twenty years' experience I was very sorry and distressed to read Dr. B. M. Newey's letter (Sept. 18, p. 574). Shipping companies and their agents in the East must be very different from what they are elsewhere in the world. During the above long experience I have looked after the seriously sick, the insane, the suicidal, and even the criminal on board ship, and I cannot recollect ever refusing a case. I have even accepted the urgently ill from other ships on the high seas.

Indeed, I would say to Dr. Newey, "*Audi alteram partem.*" About a year ago, from the R.N. Hospital of a British dependency which shall be nameless I received a brief note that a case of "carbuncles and cirrhosis of the liver" was coming on board. I was not given a chance of even seeing, let alone declining, the case. This was in the afternoon. The patient with his wife arrived at the ship's side at 9 p.m., within a few hours of sailing, having sold up hearth and home. I could not have refused him even had he been on the point of death. Examination in the surgery showed five large active carbuncles, two of them over four inches in diameter. He showed the typical signs of hepatic cirrhosis: hard, enlarged liver; jaundice; oedema; sallow complexion. His wife, who was present, was quite shocked. It appeared that she had insisted on taking him out of hospital; but she stated that had his condition been revealed to her (which apparently it had not been) she would not have done so. I am inclined to think that his removal from hospital was not unacceptable to those in charge.

Fortunately I had an ample supply of penicillin on board, and under large doses of this the carbuncles healed in a remarkable way. A few days later, however, his cirrhosis advanced, jaundice deepened, oedema increased, and he died within a few days of reaching the U.K.

Experiences of this kind (fortunately very rare) do not promote "friendliness, delight at receiving case notes, and willingness to accept responsibility."—I am, etc.,

Bridge of Weir, Renfrewshire. JOHN S. MEIGHAN.

POINTS FROM LETTERS

Shortage of Nurses

Mr. W. S. BRINDLE (Hyde, Cheshire) writes: Mr. L. H. Hornsby, director of public relations to the Ministry of Labour and National Service, writes (Sept. 25, p. 622), "In his letter Dr. N. Strang states that the numbers of nurses in employment in this country are dwindling. Nothing could be further from the truth." Could it not? What about, "The numbers of nurses in employment in this country have dwindled to none"? Presumably Mr. Hornsby meant, "This is wrong." This saves four words and twenty-two letters. Perhaps *Plain Words*, by Sir Ernest Gowers, has not yet found its way to the Ministry of Labour and National Service.

Traumatic Amputation

Dr. G. O. M. DICKENSON (Haslemere, Surrey) writes: When a "dresser" at the Royal Infirmary, Newcastle-upon-Tyne, in 1897 or 1898 I remember a man being admitted with evulsion of one arm at the shoulder. The traumatic amputation was completed by snipping through a strip of skin about an inch wide. There was very little bleeding. I expect the wound was dressed with perchloride or cyanide gauze, and to the resulting granulating surface skin grafts were applied—each dresser supplying a piece from his own arm. The patient, a burly Irishman, did not take amiss the remarks that he now possessed a bit of good English skin. His recovery was complete and uneventful.

Oil Baths in India

Dr. T. N. S. RAGHAVACHARI (Madras, India) writes: May I supplement the observations of Dr. Percy E. Turner (April 17, p. 758)? There is a popular old vernacular proverb current in this land which says, "Instead of paying heavy fees to the doctor, pay a small sum regularly to the oil-monger and keep fit." The idea underlying this is that systematic oil baths twice a week keep one free not only from skin affections but also from several ills to which flesh is heir. The oil intended for the anointing is often heated well in an iron pan, with the addition of bits of turmeric (the dried rhizome of which is bright yellow in colour and reputed to be rich in carotene and to possess healing properties), a few grains of black pepper, and half a spoonful of cumin seeds. Oil baths have been a great institution in South India and in Bengal too. Expert masseurs are employed by the rich to give them a real good massage with the oil, which is liberally anointed over their bodies. In Travancore, Cochin, and Malabar daily inunctions with simple coconut oil in the case of normal individuals and variously medicated oils in the case of persons suffering from different ailments (particularly those involving the joints and muscles) have for long been and continue to be the most sought-after and popular methods in regular use for keeping fit and for restoring tone to the entire system. Sir Robert McCarrison in his wonderful little popular treatise on food speaks very highly of oil baths taken in diffuse sunlight at regular short intervals, as these help considerably to provide vitamin D to the system most naturally and efficiently. An ancient custom of the Hindus is to keep gingelly and coconut oils in big mud pots immediately after the oils are expressed in a wooden mill and leave them exposed to direct sunlight in the open courtyard for a full day or two before storing them in their larders.

Vitamin K and Chilblains

Dr. DAVID P. WHEATLEY (Twickenham) writes: Further to my communication on this subject printed in the *Journal* of Nov. 1, 1947 (p. 689), I append some further experiences in this treatment which may be of interest to anyone wishing to try the method. Using a water-soluble preparation (2-methyl-1 : 4 naphthohydroquinone disuccinate) I have not encountered any pain on intramuscular injection. However, I have found oral administration of 20 mg. t.d.s. so effective that I no longer use the intramuscular route. There is a time lag of 4–5 days before any effect is noticeable, and it is only occasionally that the dose can be reduced below this level. Children should not be allowed to suck or chew the tablets, as otherwise a moderate glossitis develops, which, however, rapidly clears on cessation of the practice.

Obituary

C. M. WENYON, C.M.G., C.B.E., F.R.S.

By the death of Charles Morley Wenyon on Sunday, Oct. 24, British medicine loses one of its foremost protozoologists and one of its most interesting characters. He was the eldest son of Charles Wenyon, M.D., a pioneer medical missionary in Southern China, and was born in Liverpool in 1878. Much of his early childhood was passed in China, in Fatshan, and in moments of stress he was apt to express his thoughts in what he said was Chinese. Wenyon came back to England in 1892 to Kingswood School, Bath, and began his professional studies at Leeds University, later transferring to University College and Guy's Hospital. He obtained a B.Sc. in 1901, and graduated M.B., Ch.B. in 1904. Almost at once he took up the subject of medical protozoology, and in 1905 was appointed protozoologist to the London School of Tropical Medicine, where, in the old Dock Hospital, Sir Patrick Manson was then at the height of his fame. In the following two years Wenyon visited the Sudan, studying trypanosomiasis and malaria; this was his first contact with Sir Andrew Balfour, with whom he was later intimately associated for so many years. Later he wandered over the Middle East from Bagdad to Malta, studying leishmaniasis, which remained for many years one of his major interests.

He returned to the London School of Tropical Medicine, and in 1914 joined the Wellcome Bureau of Scientific Research which had just been founded by Dr.—later Sir Henry—Wellcome, with Dr. Andrew Balfour as its first director. Within a few months of its foundation both Balfour and Wenyon were seconded for military service. Before the outbreak of war in 1914 the current teaching had been that almost all the dysentery in the Middle East was due to *Entamoeba histolytica* and very little to bacillary dysentery. As a result, in the Gallipoli theatre patients suffering from dysentery were being treated with large doses of emetine, and the death rate was in consequence high. Wenyon's investigations in Egypt clearly demonstrated that the greater proportion of cases of dysentery were not due to amoebae; emetine thus ceased to be given as a routine to every patient and countless lives were saved. Wenyon summarized the results he had obtained in the Near East, which is now referred to as the Middle East, in a valuable work written in 1917 in collaboration with F. W. O'Connor, *Human Intestinal Protozoa in the Near East.* In addition he was responsible for the protozoological sections in the first edition of *Memoranda on Medical Diseases in Tropical and Subtropical Areas,* a compilation published by command of the Army Council which has been of inestimable benefit to medical officers in two world wars.

His next task was to investigate the malaria which was completely immobilizing the Allied Forces in Salonika. With the tools at hand it was obviously impossible to deal with malaria in the ways in which it was later overcome in the second world war, but Wenyon's reports had two important results: they served to discourage any further bellicose adventures by the British in the Balkans, and they emphasized the total inadequacy of the measures then available for the treatment and prevention of malaria. Largely through his continued interest in malaria in the Balkans Wenyon prevailed on Sir Henry Wellcome to support in this area a small laboratory, which under Dr. Henry Foy has carried out much important work on blackwater fever. After having acted as consultant in malaria both to the British Salonika Forces and after 1918 to the Army of the Black Sea, Wenyon returned to the Wellcome Bureau of Scientific Research in 1920. For his war services he was made C.M.G. and C.B.E.

When Sir Andrew Balfour became the first director of the newly founded School of Hygiene and Tropical Medicine in 1923 Wenyon naturally succeeded him as director of the Wellcome Bureau of Scientific Research, and when in its turn the Wellcome Research Institution arose in the Euston Road he became its first director-in-chief as well as director of research to the Wellcome Foundation. In 1926 Wenyon published his treatise on medical protozoology—"a manual for medical men, veterinarians, and zoologists"—which, as was most justly due, was at once hailed as a standard work. The effort expended in compiling these two magnificent volumes seems largely to have exhausted his capacity for research, and thereafter he published little that was original. His time, however, was fully occupied. In addition to directing an important research institution he had become in 1920 an honorary secretary of the Royal Society of Tropical Medicine. It was largely as a result of his initiative and drive that Manson House was built and freed from debt, and his endeavours were also largely responsible for the present flourishing condition of the Royal Society of Tropical Medicine. In 1945 he was elected president of the Society, and in 1947 was awarded its Manson Medal. Since 1920 he had acted as a sectional editor of the *Tropical Diseases Bulletin.* It is thus hardly surprising that in the course of years he became a kind of final court of appeal on all matters protozoological. This entailed a constant stream of visitors to the Wellcome Bureau from the Commonwealth, the Continent, and the United States of America.

Wenyon received many honours in addition to those already mentioned. In 1927 he was elected a Fellow of the Royal Society. He was also an associate member of the Société de la Pathologie Exotique, and in 1933 became an officer of the Legion of Honour. In 1945 he was elected an honorary life member of the New York Academy of Sciences, and in 1946 the American Society of Tropical Medicine awarded him the Theobald Smith Gold Medal. Finally, in 1947, he was elected an honorary fellow of the Royal Society of Medicine.

Although Wenyon made no outstanding medical discovery—his most important were probably the differentiation of *Endolimax nana* from other intestinal protozoa and the discovery of two of the five intestinal flagellates of man—yet he will have an assured place in the history of medicine. He it was who, with his old friend Professor Brumpt, still happily with us, first established protozoology as an essential branch of medical parasitology. Under his aegis the Wellcome Bureau of Scientific Research became internationally known. As the director of a scientific institution he can have had few equals, for he possessed in no uncertain degree the by no means common knack of invariably keeping "a happy ship." Those who worked with him will recall his, "Well! I don't know, I'm sure. What?"

In 1944 Wenyon retired from the Wellcome Research Institution but continued to act as consultant in tropical medicine to the Wellcome Foundation. For many years he had been collecting notes and material for a second edition of his *magnum opus,* but only a few days before his death he had reluctantly informed his publishers that to accomplish his task was beyond his strength. It is to be hoped that younger hands will be enabled to bring his work to its final fruition.—G. M. F.

PERCIVAL P. COLE, O.B.E., M.B., F.R.C.S.

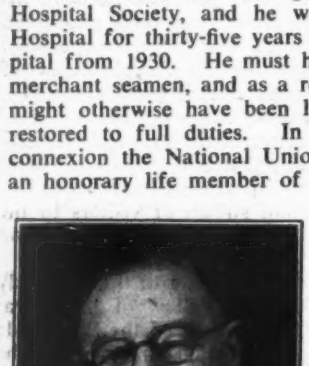
After a long and trying illness, Percival Pasley Cole died in London on Oct. 19.

Percival P. Cole was born at Weymouth on March 4, 1878, and educated at Weymouth College. He entered Guy's Hospital in 1897 as a dental student, and qualified in 1899. He decided to become medically qualified, and obtained the Conjoint diploma in 1904. He held several house appointments at Guy's Hospital and took the F.R.C.S. in 1906. He then became lecturer in anatomy at Birmingham University, and there he graduated M.B., Ch.B. in 1909. On his return to London Cole first worked as demonstrator of anatomy at the Middlesex Hospital, and then quickly obtained several hospital appointments, becoming surgeon to Queen Mary's Hospital for the East End in 1911, surgical registrar at the Cancer Hospital in the same year, and assistant surgeon to the Dreadnought Hospital the following year. He maintained his connexion with these three hospitals to the end, becoming senior surgeon to Queen Mary's Hospital in 1932 and consulting surgeon in 1938. At the Cancer Hospital he was appointed assistant surgeon in 1920, surgeon in 1922, and consulting surgeon in 1946. He became full surgeon at the Dreadnought Hospital in 1919, consulting surgeon in 1947, and vice-president in 1948.

Cole's early dental training may have accounted for his interest in plastic surgery, and throughout the 1914–18 war he was honorary surgeon to King George's Hospital, Waterloo

Road, and in charge of maxillo-facial cases, and he was also on the staff of the Brook War Hospital. At this time he published several articles on war injuries to the face and jaws, on other types of war wounds and injuries, and on reparative surgery.

Percival Cole was also greatly interested in the Seamen's Hospital Society, and he was surgeon to the Dreadnought Hospital for thirty-five years and surgeon to the Tilbury Hospital from 1930. He must have operated upon thousands of merchant seamen, and as a result of his care many men who might otherwise have been lost to the Merchant Navy were restored to full duties. In recognition of his work in this connexion the National Union of Seamen in 1946 made him an honorary life member of the Seamen's Union. Cole was the first member of the medical profession ever to be accorded this honour. As recently as July of this year he was made a vice-president of the Corporation of the Seamen's Hospital Society, which was the highest honour that Corporation could bestow. He recently took part in the preparation by the Board of Trade of the eighteenth edition of the *Ship Captain's Medical Guide*, which originally dates from 1868.



[*Elliott and Fry, Ltd.*

From 1926 Cole was consulting surgeon to the Bethnal Green Hospital, and he served on the executive council of the Institute of Hygiene from 1931. He continued in that capacity in the present Royal Institute of Public Health and Hygiene. He was Hunterian Professor of the Royal College of Surgeons in 1918 and a member of the Association of Plastic Surgeons. He was awarded the O.B.E. in the New Year's Honours List of 1947.

Cole was specially interested in several branches of surgery. For many years he was the chief exponent in this country of the filigree operation for inguinal and other herniae. In fact he was one of the early pioneers in the use of non-absorbable monofilament sutures. He advocated and used this type of suture when many others were still doubtful of its value. Before the days of radiotherapy he brought relief to many cases of cancer of the uterus by his patient application of the "cold cautery." His skill as a first-class cancer surgeon and his wide knowledge of plastic surgery benefited many cases of the most distressing types of cancer. He was a competent and pleasant teacher and devoted much time and thought to the organization of postgraduate courses for ship surgeons. Throughout the British Commonwealth hundreds of his residents and postgraduate students remember him with gratitude and pride. During and since the second world war he continued his indefatigable work till well over the age at which he could have retired, and those who sought his counsel found knowledge and wisdom and a sure grasp of affairs remarkable in a man over 70 years of age.

Although his passage through life was sometimes turbulent, Cole was always fearless and single-minded. His friends, colleagues, and associates found him easy to approach and received from him a ready sympathy combined with a wide sense of justice and a tolerance for others which won for him a lasting admiration and affection. The sympathy of all his many friends will be extended to his son and daughter by his first wife, and to his widow, Dr. Pearl Greene, of the Marie Curie Hospital.

Mr. E. T. C. Milligan writes: The passing of Percival P. Cole removes from the surgical world a colourful figure and leaves a sad gap in a wide circle of friends. His sayings and writings were a delight, for he had the gift of the picturesque word, the polished phrase, and deep feeling. It was perhaps easier for him to share his plans and ideas than his heart. He had strong views and rigid opinions, and for these he fought in the face of opposition and at the risk of criticism. No one was better fitted to champion the new revolutionary treatment of hernia by filigrees. At the Dreadnought Hospital in the early part of this century he learnt the operation from Lawrie McGavin. He saw in it a method which alone in those days could deal successfully with a sailor's hernia and return him to sea. P.P. never wavered in his assessment and appreciation of this operation, and while new fashions followed one after another he maintained his confidence and enthusiasm for the filigree method. He practised it, taught it, and had it filmed—a film which should be preserved as a record of successful pioneering work, for now surgical opinion is no longer unkind to the filigree and buried metal.

Usually, as surgeons mature, wider visions for closer human and world relationships call them. The scientific world of surgery alone ceases to satisfy their heart's longings. Percival Cole, however, maintained his interest in surgery and surgical technique at white heat, so that the planning and execution of his jaw and face surgery, his filigree repair of the largest hernias, and his bold operations for cancer continued to be done with finished artistry and tenderest touch. His individual concern and care for sick merchant sailors of all nations through the Seamen's Hospital Society were an inspiration to his colleagues. He showed that through medicine it was possible to surmount the antipathies of class, colour, and nations. We will remember him as a man who knew what he fought for and loved what he knew. P.P. gave an inspiring lead and was a great fighter.

Dr. Henry Robinson writes: Percival Cole was the junior, and the last survivor, of the surgical team which in the second and third decades of the century drew visitors from far and near to the clinics and the operating theatres at the Royal Cancer Hospital—the others of the sextet were Charles Ryall, Ernest Miles, Jocelyn Swan, Cecil Rowntree, and Cecil Joll. While all were first-rate general surgeons, several of them had special interests—Miles in proctology, Swan in genito-urinary work, Joll in thyroid and gastric surgery. Coles's special line was plastic surgery, in which he got ample opportunities of serving his generation in both the two great wars. No doubt his early training as a dental surgeon was of value in facial reconstructions; but apart from this he had a real flair for this specialty and had both the imaginative boldness in planning and the deftness in execution which plastic surgery requires. He was a consistent exponent of Arbuthnot Lane's "no touch" technique, which he practised as admirably as Lane himself. Cole was a good committee-man and a born chairman; though he suffered fools not very gladly, and could be rather tart if he thought nonsense was being talked, he knew how to keep a meeting to the point and not allow it to wander off into side issues. He was of athletic frame and had been good at several games, notably lawn tennis.

SIR BRUCE BRUCE-PORTER, K.B.E., C.M.G., M.D., D.L.

Sir Bruce Bruce-Porter died on Oct. 15 at the age of 79 at the home of his son-in-law and his daughter in Somerset. Harry Edwin Bruce Bruce-Porter was the son of the late Capt. J. Porter, R.A., and was born at Woolwich. He was educated privately and at the London Hospital, where he won many prizes and scholarships. He qualified as L.S.A. in 1892, and took the Conjoint diploma in the following year. He then joined the Army Medical Staff, as it was called, and won more distinctions at Netley. After rising to the rank of surgeon-captain he resigned and began private practice in the West End of London. As Dr. Bruce-Porter he was soon well known, and at one time had probably one of the largest and most lucrative general practices in London. He was one of the men who were quick to appreciate the value of the young science of clinical pathology. His opportunity for distinction came with the war of 1914–18, when he was recalled to service and promoted to command the Third London General Hospital, where he found himself at the head of a team of the leading London consultants. Later he went out to Mesopotamia in command of No. 40 British General Hospital, was mentioned in dispatches, and awarded the C.M.G. in 1917. He had also done good work as physician to King Edward VII's Hospital for Officers.

Outside his strictly professional work Bruce-Porter had many interests and made himself very useful. He was a Deputy-Lieutenant for London, a Fellow of the Institute of Public

Health, a member of the Council of the Imperial Service College Trust, a military member of the Council of the Territorial Force Association of London, a past president of the Hunterian Society, a vice-president of the Shaftesbury Society and Ragged School Union, an honorary member of the Smeatonian Society of Civil Engineers, and a Knight of Grace of the Order of St. John of Jerusalem. He served also on a Home Office committee charged with inquiry into legislation on the treatment of inebriates. He founded the Bruce-Porter Home for children of Dr. Barnardo's Homes needing orthopaedic treatment. In 1919, then a colonel in the Army Medical Service, he was honoured for his services by the conferment of the K.B.E. In later years he joined forces with Sir Arbuthnot Lane in the latter's New Health Society.

Sir Bruce married in 1896 Essie, daughter of the late Rev. D. Bruce, D.D., of Auckland, New Zealand, and widow of J. H. Honeyman, M.D. They had twin daughters. Lady Bruce-Porter was a Lady of Grace of the Order of St. John of Jerusalem, and died in 1937. Bruce-Porter had been an early and keen devotee of motoring, and was a founder-member of Brooklands.

Dr. William Henry Lewis, who died on Sept. 24 at the age of 82, was born at Llansantffraid and lived and worked there all his life. A student at the University of Edinburgh, he graduated M.B., C.M. in 1887, and was still only 21 when he returned to Llansantffraid and went into practice. In the course of forty-two years in general practice Dr. Lewis won the esteem and affection of thousands of patients. He retired from practice in 1929, and was then able to devote much of his time to local government. He had become a county councillor in 1919, and was for many years chairman of the public health committee, and took a particular interest in the problems of mental deficiency, tuberculosis, and school medical services. He represented the county on the Court of the University of Wales and on the board of the Normal Training College, Bangor. He had been appointed a justice of the peace as early as 1904, and in recognition of his long service to the county he was appointed high sheriff of Montgomeryshire in 1935. Dr. Lewis had two hobbies, gardening and wood-carving. He carved the reredos at Llansantffraid Church, and many notable examples of his carvings of furniture are still to be found in the district. Dr. Lewis had been a member of the British Medical Association for almost sixty years, and he served as president of the Shropshire and Mid-Wales Branches in 1927–8. He was also vice-president of the North Wales Society for the Blind.

Dr. Arnold Thomas Densham, the son of Henry Densham, of Bristol, died in London on Oct. 13, at the age of 66. He was educated at Clifton College and St. John's College, Cambridge. After leaving Cambridge he entered Guy's Hospital and the Royal Ear Hospital, Soho. Densham entered the Indian Medical Service and remained abroad until invalided out in 1909. The disability which led to his resignation was deafness following diphtheria contracted while attending a patient. Densham did not feel justified in continuing medical work under such a disability; the difficulty in hearing heart and chest sounds was to his mind incompatible with medical practice, although other work in the service had been suggested to him. Dentistry seemed to offer a branch of medical work which he could undertake, and no doubt he was influenced in this choice by having a brother, Ashley, in the dental profession, whom he subsequently joined in practice. This entailed his return to Guy's Hospital in 1909 in order to take a dental qualification, which he accomplished in 1911. Subsequently he held for some years the appointment of chief assistant in the dental department of St. Bartholomew's Hospital. Densham had a sound knowledge of medicine, was a good classical scholar, and a knowledgeable man in many other respects, always able to give a sound and well-considered opinion. He used short rather than long words if equally applicable, and had the gift of expressing much in a few clear and concise phrases. In this respect he resembled his uncle, George Ernest Herman, whose book on difficult labour was often quoted as a model of clear and concise language. Densham's sense of fairness and his integrity of character were shown in many ways during his life, quite apart from his characteristic refusal to continue in a service in which he considered he was unable to give his best. Densham was a lovable character, modest in every way and courteous in manner. His disability made it difficult for him to enter much into society, but his friends, though few, were very appreciative of his fine and generous qualities. He was a bachelor, and the youngest but one in a family of eleven.

Dr. Frederick Robert Dingle, who died with tragic suddenness on Oct. 2, at the age of 46, was a student at Guy's Hospital, and qualified M.R.C.S., L.R.C.P. in 1925. He went to Gateshead a few years later and quickly built up a large practice. His popularity as a doctor in a densely populated industrial area meant that he had to work very hard. During the war years, despite the added burden of being entirely without assistance, he did his full share in the work of the protection of practices scheme, and his obligations to his absent colleagues were most faithfully fulfilled. Dr. Dingle still found time for outside activities in the medical field. He was chairman of the Gateshead Division of the British Medical Association in 1940–1, but perhaps his greatest outside interest was in his work for the Medical Institute in the sister borough of Newcastle-upon-Tyne. He was treasurer of this popular doctors' club from 1937 until his death, and over this ten-year period there was a remarkable development in every field of the Institute's activities, largely as a result of Dr. Dingle's work. His early death will be deeply regretted not only by his many patients but also by his fellow practitioners in the North-east.—J. C. A.

Dr. Eric Oliver Blake died at his home in University Square, Belfast, on Sept. 24 after a few months' illness. Dr. Blake, who was a native of Trinidad, came to Belfast in 1922 and graduated there in 1927. Soon afterwards he started in general practice in the Newtownards Road district.

D. B. E. writes: Dr. Blake will long be remembered by his many patients and friends for his kindness, particularly to the poor, and for his devotion to duty. He was a good physician and one of the best type of general practitioner. The sympathy of his colleagues in Belfast will be extended to his wife and to the rest of his family.

Dr. Alexander Boyd Roberts, who died on Oct. 7 at the age of 74, was in practice in Hammersmith and Maida Vale for thirty years before ill health forced him to retire in July of this year. In his native Canada he was better known as one of the intrepid men who led the Klondike Gold Rush in 1896. With his brother James he was among the first to cross the Chilkoot Pass, and at Lake Bennett they built their own boat, *The Clyde*, one of the steadiest craft to run the Whitehorse. Roberts learnt to the full the dangers and hardships of the North, and came from the Klondike with a life already packed with experience. Soon afterwards he began his medical studies, and graduated M.D. at McGill University, Montreal, in 1902. He practised in Saskatoon until the 1914–18 war, when he served in the C.A.M.C. and later in the R.A.M.C. During the recent war he was medical officer to a first-aid post in Paddington, where he gave invaluable service. In his work his greatest interest always lay with his patients. He was an outstanding general practitioner of the best type, and his enforced retirement was felt by his patients as a great loss to them all. He married Dorothy Brand-Hardy, of Beckenham, Kent, in 1916, and she and a married daughter in France survive him. His last years were clouded by the loss of his only son and younger daughter.

Dr. Lyster Cole-Baker died at his home in Waterlooville, Hants, on Oct. 14, at the age of 83. Dr. Cole-Baker was born in Victoria, Australia, and studied medicine at Trinity College, Dublin, in London, and in Vienna. He graduated at Dublin in 1890, and proceeded M.D. two years later. He spent a year in practice in Maidstone before settling in Portsmouth, where for many years he was honorary ophthalmic surgeon at the Eye Infirmary and honorary surgeon at the Royal Portsmouth Hospital. During the 1914–18 war he was in charge of the Military Families' Hospital there. Dr. Cole-Baker is said to have been responsible for introducing the principles of aseptic surgery at the Royal Hospital. He was a frequent contributor to the medical press, and published short articles in the *Journal* as long ago as 1901. He was one of the first doctors in the city of Portsmouth to own a motor-car, and he had been a councillor for many years, retiring only when he was appointed school medical officer at Waterlooville. During the second world war he joined the Home Guard, and was A.R.P. casualty officer for his district. For many years Dr. Cole-Baker was actively concerned with the Portsmouth Conservative Association and a member of the Royal Albert Yacht Club.

Dr. Charles Dudley Bishop, who died on Oct. 17 at the age of 73, was one of the older generation of doctors in Wandsworth. A native of Clapham, he was a student at Charing Cross Hospital, and qualified in 1899. He remained in general practice throughout his lifetime, and was held in great respect and esteem by his colleagues and his patients alike. Before the war he acted as honorary anaesthetist at the Bolingbroke and

Charing Cross Hospitals, and his many years of service in that capacity are recalled with gratitude. As a younger man he took a keen interest in local medical affairs. He was a loyal member of the British Medical Association, which he first joined in 1901. He represented his colleagues at the annual representative meetings in 1925, 1926, and 1927, and was chairman of the Wandsworth Division from 1930–2. Though he continued in practice until recently, failing health curtailed his activities. In spite of that he contrived to be a regular attendant at the divisional meetings during the controversial months preceding the introduction of the National Health Service. His wife, who died three or four years ago, was a chronic and almost helpless invalid, and the devotion and care which he bestowed upon her were most touching. He was a genial, kindly man, a general practitioner in the best traditions of the old school, and his familiar figure will be greatly missed.

Universities and Colleges

UNIVERSITY OF CAMBRIDGE

Sir Walter Hamilton Moberly, chairman of the University Grants Committee, will deliver the Rede Lecture in the Senate House on Thursday, Nov. 18, at 5.30 p.m. His subject is "Universities and the State."

UNIVERSITY OF LONDON

Dr. H. R. Ing, D.Phil., will deliver a Special University Lecture on "The Pharmacology of Homologous Series" at the London School of Hygiene and Tropical Medicine, Keppel Street, W.C., on Friday, Dec. 3, at 5.15 p.m. The lecture is addressed to students of the University and to others interested in the subject. Admission is free, without ticket.

The Semon Lecture for 1948 entitled "Broncho-oesophagology in Great Britain—the Decline of a Science: A Plea for Better Co-operation and Teaching" will be delivered by Mr. G. Ewart Martin at the Royal Society of Medicine (1, Wimpole Street, London, W.) on Thursday, Nov. 4, at 5 p.m. Special University Lectures on "Rubella in Pregnancy as an Aetiological Factor in Congenital Malformations and Still Birth" by Dr. Charles Swan (University of Adelaide) and "Social Factors in Obstetrics" by Professor D. Baird (University of Aberdeen) will be delivered at Westminster Medical School (Meyerstein Lecture Theatre), Horseferry Road, London, S.W.1, on Tuesday, Nov. 16, at 5 p.m., and Friday, Nov. 26, at 5.30 p.m. respectively. The lectures are addressed to students of the University and to others interested in the subjects. Admission is free, without ticket.

The following candidates have been approved at the examination indicated:

ACADEMIC POSTGRADUATE DIPLOMA IN MEDICAL RADIOLOGY.—J. C. Bulstrode, J. G. L. Cole, J. C. A. L. Colenbrander, J. B. Latto, D. O'Connell, J. H. O'Connell, B. Stoll, R. D. St. G. Tucker, A. H. N. Welikala.

UNIVERSITY OF LIVERPOOL

At a graduation ceremony held on Oct. 15 the degree of Master of Radiology was conferred on J. R. MacLeod and D. E. Paterson.

UNIVERSITY OF LEEDS

Stanley Jack Hartfall, M.D., F.R.C.P., Professor of Therapeutics and Applied Pharmacology, has been appointed to the Chair of Clinical Medicine in the University, in succession to J. le Fleming C. Burrow, M.D., F.R.C.P., who has retired, and Louise Frances Winifred Eickhoff, M.D., D.P.M., has been appointed Senior Lecturer in Child Psychiatry.

QUEEN'S UNIVERSITY, BELFAST

The first A. B. Mitchell Memorial Lecture was delivered at Queen's University, Belfast, by Professor G. Grey Turner, M.S., F.R.C.S., on Oct. 19. His subject was "Transplantation of the Ureters."

ROYAL COLLEGE OF PHYSICIANS OF LONDON

The Harveian Oration was delivered at the College on Oct. 18 by Dr. F. M. R. Walshe on "The Structure of Medicine and its Place among the Sciences." The Oration was printed in an abridged form in the *Journal* of Oct. 23 (p. 753).

After the Oration the Weber-Parkes Medal and Prize were presented to Dr. Stephen Roodhouse Gloyne. The prize is awarded triennially for the best work done on the aetiology, prevention, pathology, or treatment of tuberculosis.

ROYAL COLLEGE OF SURGEONS OF ENGLAND

The Annual Meeting of Fellows and Members of the College will be held at the College (Lincoln's Inn Fields, London, W.C.) on Wednesday, Nov. 10, at 5.30 p.m., when a report from the Council will be laid before the meeting.

No. 41

INFECTIOUS DISEASES AND VITAL STATISTICS

We print below a summary of Infectious Diseases and Vital Statistics in the British Isles during the week ended Oct. 9.

Figures of Principal Notifiable Diseases for the week and those for the corresponding week last year, for: (a) England and Wales (London included). (b) London (administrative county). (c) Scotland. (d) Eire. (e) Northern Ireland.

Figures of Births and Deaths, and of Deaths recorded under each infectious disease, are for: (a) The 126 great towns in England and Wales (including London). (b) London (administrative county). (c) The 16 principal towns in Scotland. (d) The 13 principal towns in Eire. (e) The 10 principal towns in Northern Ireland.

A dash — denotes no cases; a blank space denotes disease not notifiable or no return available.

Disease	1948 (a)	(b)	(c)	(d)	(e)	1947 (Corresponding Week) (a)	(b)	(c)	(d)	(e)
Cerebrospinal fever	31	2	13	1	1	45	3	23	4	4
Deaths		—	—				—	—		
Diphtheria	112	13	45	16	1	201	18	60	11	5
Deaths	—	—	2	—	—	—	—	—	—	—
Dysentery	84	5	88	—	—	67	9	51	3	—
Deaths				—	—				—	—
Encephalitis lethargica, acute	1	—	—	—	—	2	1	—	—	—
Deaths		—					—			
Erysipelas			22	12	3			43	10	3
Deaths		—					—			
Infective enteritis or diarrhoea under 2 years				46					80	
Deaths	25	4	8	2	—	70	4	15	8	5
Measles*	4,061	79	73	85	104	1,639	50	95	151	9
Deaths†			—	—	—	—	—	1	—	—
Ophthalmia neonatorum	63	7	13	—	—	71	6	15	—	—
Deaths										
Paratyphoid fever	13	3	1 (B)	3 (B)	—	12	—	1 (A) 4 (B)	—	—
Deaths	—	—	—	—	—	—	—	—	—	—
Pneumonia, influenzal	421	27	4	2	—	403	19	3	1	2
Deaths (from influenza)‡	3	—	2	—	1	13	3	2	1	—
Pneumonia, primary			170	17				164	15	
Deaths	140	22		5	7		23		6	3
Polio-encephalitis, acute	7	—				26	3			
Deaths							—			
Poliomyelitis, acute	79	9	2	—	1	338	31	76	6	10
Deaths§	6	1					2			
Puerperal fever		—	8		—		—	8		—
Deaths										
Puerperal pyrexia‖	111	11	4	—	—	106	6	11	—	—
Deaths		—					—			
Relapsing fever	—	—			—	—	—			—
Deaths										
Scarlet fever	1,273	75	248	174	38	1,316	84	300	60	44
Deaths†			—	—	—	—	—	—	—	—
Smallpox	—	—	—	—	—	—	—	—	—	—
Deaths				—	—				—	—
Typhoid fever	18	1	—	12	—	8	1	—	18	2
Deaths	—	—	—	—	—	2	—	—	—	—
Typhus fever	—	—	—	—	—	—	—	—	—	—
Deaths				—	—				—	—
Whooping-cough*	2,073	127	64	48	13	1,043	73	40	28	2
Deaths	5	—	—	1	—	3	—	—	1	—
Deaths (0–1 year)	259	33	38	17	9	361	46	66	25	12
Infant mortality rate (per 1,000 live births)										
Deaths (excluding still-births)	4,051	638	539	157	106	4,240	676	556	147	85
Annual death rate (per 1,000 persons living)			10·9	9·8				11·6	9·3	
Live births	8,020	1340	1024	406	252	9,031	1492	1096	430	276
Annual rate per 1,000 persons living			20·7	25·4				22·1	27·1	
Stillbirths	193	19	42			216	30	42		
Rate per 1,000 total births (including stillborn)			39					37		

* Measles and whooping-cough are not notifiable in Scotland, and the returns are therefore an approximation only.

† Deaths from measles and scarlet fever for England and Wales, London (administrative county), will no longer be published.

‡ Includes primary form for England and Wales, London (administrative county), and Northern Ireland.

§ The number of deaths from poliomyelitis and polio-encephalitis for England and Wales, London (administrative county), are combined.

‖ Includes puerperal fever for England and Wales and Eire.

EPIDEMIOLOGICAL NOTES

Discussion of Table

In *England and Wales* increases were recorded in the notifications of measles 515, scarlet fever 39, and dysentery 26. There were decreases in the incidence of whooping-cough 131 and typhoid fever 22.

The largest rises in the notifications of measles were Lancashire 207 and Gloucestershire 76, and the largest fall was Yorkshire West Riding 51. No large fluctuations were reported in the local incidence of diphtheria or scarlet fever. The only variation of any size in the local trends of whooping-cough was a decrease of 50 in Essex.

The chief centres of dysentery were Lancashire 28 (Liverpool C.B. 20) and Surrey 15. The largest returns for poliomyelitis were Yorkshire West Riding 11, London 9, Middlesex 6, Surrey 6, and Lancashire 5.

In *Scotland* an increase of 29 in the notifications of dysentery and a decrease of 13 in cerebrospinal fever and of 10 in diphtheria were the chief features of the returns. The largest returns of dysentery were Glasgow 57 and Lanark county 17. The fall in the incidence of cerebrospinal fever and diphtheria was due to the experience of the western area.

In *Eire* increases were recorded in the notifications of scarlet fever 48, measles 40, and typhoid fever 10; a decrease of 11 was reported in the notifications of diarrhoea and enteritis. The rise in the incidence of scarlet fever was due to the experience of Dublin C.B. A further 55 cases of measles were notified from the outbreak in Clare, Kilrush R.D., where 28 cases were notified in the preceding week. The 12 cases of typhoid fever were scattered through nine areas; the only multiple notification was 4 cases in Kerry, Dingle R.D.

In *Northern Ireland* a decrease of 13 was recorded in the notifications of scarlet fever. In Belfast C.B. a rise of 33 occurred in the notifications of measles, while the incidence of whooping-cough declined by 11.

September Quarter, England and Wales

In the weekly return of the Registrar-General for England and Wales for Oct. 16 provisional rates are given for the September quarter. The infant mortality was 28 per 1,000 live births, and was the lowest rate ever recorded for any quarter; the previous lowest was 31 in the June quarter of this year. The stillbirth rate at 22.6 per 1,000 total births was 0.1 below the preceding lowest level. The birth rate was 17.7 per 1,000, a fall of 1.3 compared with the rate of the preceding September quarter. The general death rate was 9.4, showing a rise of 0.5 on the rate for the September quarter of 1947.

Week Ending October 16

The notifications of infectious diseases for England and Wales during the week included: scarlet fever 1,519, whooping-cough 1,949, diphtheria 141, measles 4,536, acute pneumonia 479, cerebrospinal fever 36, acute poliomyelitis 81, dysentery 114, paratyphoid 9, and typhoid 12.

Medical News

Gastro-enteritis Flying Squad

The Hospital for Sick Children, Great Ormond Street, London, has formed a flying squad of trained nurses with a medical man in charge to help in the treatment of cases of infantile gastro-enteritis in hospitals or institutions. The squad is available to visit any hospital that desires its help, and it is fully equipped to augment the existing nursing arrangements or to set up a special unit. The service starts on Nov. 1, and the squad can be obtained through the local medical officer of health or regional hospital board, or in emergency by telephoning the house governor of Great Ormond Street Hospital (Holborn 9200), who will give any further information required. The scheme is being partly financed by the King Edward's Hospital Fund and has the good will of the Ministry of Health.

Drug Tariff

The Drug Tariff (August, 1948) has now been issued in accordance with the N.H.S. (General Medical and Pharmaceutical Services) Regulations, 1948. It lists the provisions relating to the calculation of charges for drugs and appliances supplied to N.H.S. patients.

Medical Women's Federation

The address of the Medical Women's Federation is now Tavistock House (North), Tavistock Square, London, W.C.1. (Tel.: Euston 7765).

Metallic Contamination of Foods

The Ministry of Food states that the Food Standards Committee, whose appointment was announced by the Minister of Food in January, has set up a subcommittee to inquire into the metallic contamination of foods. The subcommittee is invited to consider (*a*) the available evidence of the effect of the ingestion of foods contaminated with metals or other injurious elements; (*b*) the possibility of prescribing limits of contamination; and (*c*) the technological problems which might arise from the prescription of such limits. The following have agreed to serve on the subcommittee: Mr. G. G. Barnes (Chairman); Dr. L. E. Campbell (Director, British Food Manufacturing Industries Research Association); Professor G. R. Cameron (University College Hospital Medical School); Professor S. J. Cowell (Medical Research Council); Dr. J. M. Johnston (Department of Health for Scotland); Dr. W. P. Kennedy (Ministry of Health); Dr. G. Roche Lynch (Senior Official Analyst, Home Office); Dr. J. R. Nicholls (Department of the Government Chemist); Mr. G. Taylor (Public Analyst); Dr. G. W. Monier-Williams (formerly in charge of Food Research Laboratory, Ministry of Health). The subcommittee is asking research associations, food processing firms, and medical and technical associations to co-operate in the inquiry. In particular the subcommittee wishes to know (i) the metals and the foods which have been the subject of investigation; (ii) the period covered by the investigation; (iii) the units of measure used to express the degree of contamination; (iv) the analytical method adopted. Persons or organizations who are able to supply such data and who have not already been approached are invited to write to Mr. K. R. Allen, Secretary of the Food Standards Committee, at the offices of the Ministry of Food, Food Standards Division, Devonshire House, Mayfair Place, Piccadilly, London, W.1.

Queen's University, Belfast

Latest published figures show that the amount raised for the Queen's University Centenary Endowment Fund is almost £300,000. The target figure was a quarter of a million. The Vice-Chancellor, thanking the Nuffield Provincial Hospitals Trust for its donation of £30,000 to endow a Chair and Department of Child Health, said: "The creation of the new Chair will make possible the development and integration of teaching and research facilities which exist in the hospitals associated with the University. In addition the Belfast Corporation is to make available to the University facilities for study and teaching in the child-welfare clinics. This co-ordination should advance the development of 'positive health' and result in great gain to the undergraduate teaching and postgraduate research."

Association of Certifying Factory Surgeons Dinner

At the annual dinner of the Association of Certifying Factory Surgeons, which was held at the Café Royal on Oct. 20, several speakers mentioned the necessity for team-work between management, labour, and industrial medical officers. Dr. R. Nightingale, the President, in proposing the toast to the Factory Department of the Ministry of Labour said that industry had never cried louder for help and guidance about health. There was a greater future for the certifying factory surgeon, now to be called, unfortunately in his opinion, the appointed factory doctor. Replying to the toast Mr. G. A. Isaacs, Minister of Labour and National Service, said that the fight of the trade unions to obtain improved health conditions in industry was won with the help of the doctors. The aim was now to build up a national industrial medical service properly integrated with the National Health Service. The toast of the Association was proposed by Mr. G. P. Barnett, Chief Inspector of Factories, and in reply Dr. H. W. Patterson said that he was glad that certifying factory surgeons were the legitimate children of the Ministry of Labour and the Home Office—but there was a wicked uncle in the background, the Ministry of Health. They did not want to be lost in the jungle of the various new health organizations which were being set up, and he was grateful for the help the Association had received from the B.M.A. The toast of the visitors was proposed by Dr. C. L. Graham, and Professor R. E. Lane and Dr. A. J. Amor replied.

Union of St. Luke

The Union of St. Luke has issued its first "Periodical Letter" (price 1s.). Particulars may be obtained from Dr. R. H. Hardy, 5c, Park Hill Road, London, N.W.3. The Union was founded this year as an assocation of Anglican medical men and women.

Mobile Clinics and Centres

A circular from the Ministry of Health to local authorities draws their attention to the use of mobile dental clinics and of mobile centres for maternity and child welfare. Various local authorities have been using suitably equipped vehicles for these purposes in the more remote areas where permanent centres cannot yet be provided, and information about their experience with them may be obtained from the Ministry.

Medical Clerk of a City Company

On completion of 21 years' service as Clerk of the Worshipful Company of Glaziers and Painters of Glass, Major-General R. J. Blackham, A.M.S. (ret.), has been unanimously elected an Honorary Member of the Court of Assistants—the governing body of the Company—and presented with an antique clock and a cheque by the Court and Livery of the Glaziers Company, which is distinguished from other City Guilds by representing a branch of art and not a division of industry. So far as is known General Blackham is the only medical man who has ever been Clerk of a City Company with the exception of the late Group Captain Cooper, who was Clerk of the only medical Guild—the Society of Apothecaries.

Mule Spinners' Cancer

The Manchester Committee on Cancer has recently distributed to all practitioners in the neighbourhood of the Lancashire and Cheshire cotton mills a brief account of epithelioma of the skin as it affects mule spinners which has been prepared by Dr. E. M. Brockbank. Copies are also being distributed at the request of employers and workers in some of the mills, the intention being to encourage spinners to report at the earliest stage any affections of the skin.

Wills

Dr. James McIntosh, formerly professor of pathology in London University and director of the Bland-Sutton Institute of Pathology at Middlesex Hospital, left £19,978. Dr. Alfred Walter Sikes, formerly a divisional medical officer in the public health department of the London County Council, and lecturer in physiology at King's College, left £10,298.

COMING EVENTS

Federation of Committees for the Moral Welfare of Children

The Federation of Committees for the Moral Welfare of Children (13, Gray's Inn Square, London, W.C.1) has arranged a conference to be held at Caxton Hall, Westminster, London, S.W., to-day (Friday, Oct. 29), at 2.30 p.m., when Dr. Lilias M. B. Jeffries will speak on "Marriage in Our Time," preceded by an exposition of "Our Work in Action" by committee members and a children's worker. There is a conference fee of 1s., payable on admission.

Princess Alice Emergency Hostel for Mothers and Babies

Princess Alice, Countess of Athlone, will open officially the Princess Alice Emergency Hostel for Mothers and Babies at "Castlebar," 46, Sydenham Hill, London, S.E., on Tuesday, Nov. 2, at 3.30 p.m.

Edinburgh Lectures

In connexion with the postgraduate courses in medicine and surgery the Edinburgh Postgraduate Board for Medicine has arranged a series of open lectures on subjects of wide biological interest which began in the West Medical Lecture Theatre of Edinburgh Royal Infirmary on Oct. 12. Further lectures, details of which will appear in the diary column of the *Journal*, will be given on Nov. 2 and 23 and Dec. 7 and 21. The lectures are open to all graduates and students.

Royal Dental Hospital of London School of Dental Surgery

The annual clinical "At Home" of the Royal Dental Hospital of London School of Dental Surgery will be held at the Royal Dental Hospital (32, Leicester Square, London, W.C.) on Saturday, Nov. 27, at 3 p.m. The dinner of past and present students of the hospital will be held at the Savoy Hotel at 7 for 7.30 p.m. the same day.

SOCIETIES AND LECTURES

Saturday

KENT PAEDIATRIC SOCIETY.—At Maidstone Town Hall, Oct. 30, 2.30 p.m., "*The Insecure Child*," by Miss L. M. Rendel; "*Know Your Baby*," film.

Monday

INSTITUTE OF LARYNGOLOGY AND OTOLOGY, 330–2, Gray's Inn Road, London, W.C.—Nov. 1, 2.30 p.m. "*Facial Paralysis from the Otological Standpoint*," by Miss Dorothy J. Collier.

LONDON SCHOOL OF HYGIENE AND TROPICAL MEDICINE, Keppel Street, W.C.—Nov. 1, 5.15 p.m. "*Enzymatic Break-down of Proteins (II)*," by Professor K. Linderström-Lang (Copenhagen).

SOCIETY OF APOTHECARIES OF LONDON.—In the Hall, Black Friars Lane, Queen Victoria Street, E.C., Nov. 1, 5 p.m. "*The Constitutional Factors in Psychological Medicine*," by Dr. Eliot Slater.

SOCIETY OF CHEMICAL INDUSTRY.—Joint meeting of Food Group and London Section at Royal College of Science, Huxley Building, Exhibition Road, South Kensington, London, S.W., Nov. 1, 2.15 p.m. Symposium: "*Aspects of Packaging, with particular reference to the Food Industry*."

Tuesday

CHADWICK TRUST.—At Sir Edward Meyerstein Lecture Theatre, Westminster Hospital Medical School, 17, Horseferry Road, Westminster, London, S.W., Nov. 2, 2.30 p.m. "*The Prevention of Tuberculosis, with special reference to Environment*," by Dr. Wyndham E. B. Lloyd.

EDINBURGH POSTGRADUATE BOARD FOR MEDICINE.—At Edinburgh Royal Infirmary (West Medical Lecture Theatre), Nov. 2, 5 p.m. "*Cirrhosis of the Liver*," by Professor J. W. McNee.

INSTITUTE OF DERMATOLOGY, 5, Lisle Street, Leicester Square, London, W.C.—Nov. 2, 5 p.m., "*Histopathology of the Skin*," by Dr. I. Muende.

INSTITUTE OF UROLOGY.—At St. Paul's Hospital, Endell Street, London, W.C., Nov. 2, 11 a.m., "*Manifestations of Secondary Syphilis*," by Dr. W. N. Mascall; 5 p.m., at St. Peter's Hospital, Henrietta Street, London, W.C., "*Fistula of the Bladder (Acquired)*," by Mr. F. R. Kilpatrick.

ROYAL STATISTICAL SOCIETY: RESEARCH SECTION.—At E.L.M.A. Lighting Service Bureau, 2, Savoy Hill, London, W.C., Nov. 2, 4.30 p.m. "*Some Statistical Problems Arising in Genetics*," by Professor J. B. S. Haldane, F.R.S.

SOCIETY OF APOTHECARIES OF LONDON.—In the Hall, Black Friars Lane, Queen Victoria Street, E.C., Nov. 2, 5 p.m. "*Use of Sex Hormones in Therapeutics*," by Dr. Peter Bishop.

UNIVERSITY COLLEGE, Gower Street, London, W.C.—Nov. 2, 1.15 p.m. "*Process of Learning in Octopus*," by Professor J. Z. Young, F.R.S.

Wednesday

EDINBURGH CLINICAL CLUB.—At Edinburgh Royal Infirmary (Ward 34), Nov. 3, 4 p.m. "*Leucorrhoea*," by Dr. E. C. Fahmy.

INSTITUTE OF UROLOGY.—At St. Paul's Hospital, Endell Street, London, W.C., Nov. 3, 11 a.m., "*Skin Eruptions of Secondary Syphilis*," by Dr. A. H. Harkness; 5 p.m., "*New Growths of the Bladder (Benign)*," by Mr. C. H. Mills.

LONDON ASSOCIATION OF THE MEDICAL WOMEN'S FEDERATION.—At B.M.A. House, Tavistock Square, W.C., Nov. 3, 8.30 p.m. "*Criminal Courts and the Doctor*," by Mr. Claude Mullins.

LONDON COUNTY MEDICAL SOCIETY.—At Lambeth Hospital, Brook Drive, S.E., Nov. 3, 3 p.m. Clinical meeting.

ROYAL INSTITUTE OF PUBLIC HEALTH AND HYGIENE, 28, Portland Place, London, W.—Nov. 3, 3.30 p.m. "*The Planning of a Modern School in Relation to the Public Health*," by Mr. S. Johnson-Marshall, B.Arch., A.R.I.B.A.

Thursday

EDINBURGH ROYAL INFIRMARY.—Nov. 4, 5 p.m. "*Carcinoma of Rectum*," Honyman Gillespie Lecture by Mr. Robert Mailer.

INSTITUTE OF DERMATOLOGY, 5, Lisle Street, Leicester Square, London, W.C.—Nov. 4, 5 p.m., "*Complications in Eczema*," by Dr. G. B. Mitchell-Heggs.

INSTITUTE OF LARYNGOLOGY AND OTOLOGY, 330–2, Gray's Inn Road, London, W.C.—Nov. 4, 2.30 p.m. "*Diseases of the Antrum of Dental Origin*," by Mr. J. Angell James.

INSTITUTE OF UROLOGY.—At St. Paul's Hospital, Endell Street, London, W.C., Nov. 4, 11 a.m., "*Skin Diseases Simulating Secondary Syphilis*," by Dr. A. H. Harkness; 5 p.m., "*New Growths of the Bladder (Malignant)*," by Mr. C. H. Mills.

LONDON JEWISH HOSPITAL MEDICAL SOCIETY.—At London Jewish Hospital, Stepney Green, E., Nov. 4, 3 p.m. "*The Aesthetics of Vision*," Presidential address by Mr. Harold A. Levy.

LONDON UNIVERSITY.—At Royal Society of Medicine, 1, Wimpole Street, London, W., Nov. 4, 5 p.m. "*Broncho-oesophagology in Great Britain—The Decline of a Science: A Plea for Better Co-operation and Teaching*." Semon Lecture by Mr. G. Ewart Martin.

ST. GEORGE'S HOSPITAL MEDICAL SCHOOL, Hyde Park Corner, London, S.W.—Nov. 4, 4.30 p.m. "*Neurology and Psychiatry*." Lecture-demonstration by Dr. Anthony Feiling.

Friday

LONDON CHEST HOSPITAL, Victoria Park, E.—Nov. 5, 5 p.m. "*Surgery of the Oesophagus*," by Mr. V. C. Thompson.

LONDON UNIVERSITY.—At University College (Anatomy Theatre), Gower Street, W.C., Nov. 5, 5 p.m. "*Relations of Interdependency between Various Parts of the Nervous System in the Embryo and in the Adult*." Special University Lecture (in French) by Professor G. Levi (University of Turin).

ROYAL INSTITUTE OF PHILOSOPHY.—At University Hall, 14, Gordon Square, London, W.C., Nov. 5, 5.15 p.m. "*Morality and Art*," by Professor T. E. Jessop.

ROYAL MEDICAL SOCIETY, 7, Melbourne Place, Edinburgh.—Nov. 5, 8 p.m. Debate.

SOCIETY OF APOTHECARIES OF LONDON.—In the Hall, Black Friars Lane, Queen Victoria Street, E.C., Nov. 5, 5 p.m. "*Endocrinology and its Relation to Diagnosis and Therapeutics*," by Professor E. C. Dodds.

APPOINTMENTS

Norman Fraser Mackenzie, M.B., Ch.B., Dipl.Psych., has been appointed Medical Superintendent of Newchurch Homes, Culcheth. He will also be responsible for the medical supervision of the smaller mental deficiency establishments in the Region and for advising on mental deficiency problems.

ANDERSON, H. A., L.R.C.P. and S.Ed., Medical Officer, Dingleton Hospital Melrose, Roxburghshire.

ANDERSON, MARY J. B., M.B., Ch.B., Maternity and Child Welfare Officer for Greenock.

DRUMMOND, J. S., M.B., Ch.B., D.P.H., Medical Officer, Mansfield.

GRANT, C., M.B., Ch.B., D.P.H., Senior Medical Officer of Health for Essex

GRANT, E. I., M.R.C.S., L.R.C.P., Assistant M.O.H. and Schools Medical Inspector for Wallasey, Cheshire.

LEITCH, I. D., M.B., Ch.B., Assistant Medical Officer of Health for South Shields.

LYCETT, C. D. L., M.B., B.S., D.P.H., Deputy Medical Officer of Health for the Boroughs of Chelsea and Kensington.

PORTER, C., M.D., M.R.C.P., Temporary Medical Officer for Bethnal Green, London, E.

RAVEN, R. W., O.B.E., F.R.C.S., Honorary Visiting Surgeon to the Star and Garter Home for Disabled Sailors, Soldiers, and Airmen, Richmond, Surrey.

ROBERTS, G. W., M.B., B.Ch., D.P.H., Deputy Medical Officer and Deputy School Medical Officer for Caernarvonshire.

SEWELL, E. M., M.B., Ch.B., Assistant Medical Officer of Health for Greenock.

BIRTHS, MARRIAGES, AND DEATHS

BIRTHS

Angell.—On Oct. 13, 1948, at Queen's Gate Clinic, London, S.W., to Enid, wife of Dr. C. L. Angell, a daughter.

Bulstrode.—On Oct 19, 1948, at Hartfield House, Hartfield, Sussex, to Jacqueline, wife of Dr. John C. Bulstrode, a daughter.

Naidoo.—On Oct. 19, 1948, in London, to Sandhya Bose, M.A., D.Ed.B., wife of Dr. D. Naidoo, M.R.C.P.Ed., D.C.H., a daughter—Thoruna Maya.

MARRIAGE

Hutton—Donald.—On Oct. 14, 1948, at Glasgow, Hugh Hutton, L.R.C.P.&S Ed., L.R.F.P.S.Glas., of Silloth, Cumberland, to Maie Dunlop Donald.

DEATHS

Bishop.—On Oct. 17, 1948, at 60, North Side, Clapham Common, London, S.W., Charles Dudley Bishop, M.R.C.S., L.R.C.P.

Bruce.—On Oct. 22, 1948, at Auchernack, Forres, Morayshire, John Bruce, M.B., C.M.Ed.

Bruce-Porter.—On Oct. 15, 1948, in Somerset, Sir Harry Edwin Bruce Bruce-Porter, K.B.E., C.M.G., M.D., of 22, Cranmer Court, London, S.W., aged 79.

Cole.—On Oct. 19, 1948, in London, Percival Pasley Cole, O.B.E., F.R.C.S.

Cole-Baker.—On Oct. 14, 1948, at Yew Tree Cottage, Waterlooville, Hants, Lyster Cole-Baker, M.D., aged 83.

Densham.—On Oct. 13, 1948, Arnold Thomas Densham, B.Ch., M.R.C.S., L.R.C.P., L.D.S., aged 66.

Ellis.—On Oct. 21, 1948, at Bodorgan, Anglesey, Evan Lloyd Ellis, M.R.C.S., L.R.C.P., aged 34.

Govan.—On Oct. 17, 1948, at Cockermouth, Cumberland, George Govan, M.B., C.M.Ed., aged 84.

Innes.—On Oct. 16, 1948, Edward John Innes, M.B., B.S., Flight-Lieutenant R.A.F., of 39, Murray Road, Northwood, Middlesex, aged 26.

Lankester.—On Oct. 13, 1948, Cecil Pryor Lankester, M.R.C.S., L.R.C.P., of Woodhill, Peaslake, Surrey.

Macfie.—On Oct. 11, 1948, at St. Leonard's, John William Scott Macfie, D.Sc., M.B., Ch.B.Ed., D.T.M., aged 69.

McVittie.—On Oct. 14, 1948, at Symnells, Aldington, Kent, Arthur Craigie McVittie, M.B., B.Ch., B.A.O.

Oppenheim.—On Oct. 20, 1948, at 28, Seymour Road, Crumpsall, Manchester, Bernard Oppenheim, L.M.S.S.A., aged 33.

Pallett.—On Oct 16, 1948, William Horner Pallett, M.B., Ch.B.Ed., of The Brow, Wylam-on-Tyne, Northumberland, aged 62.

Pinch.—On Oct. 14, 1948, at Bideford Hospital, Albert Edwin Hayward Pinch, M.D., F.R.C.S., Captain I.M.S. retired, aged 81.

Richards.—Recently, at Langho, near Blackburn, Beresford Tom Richards, M.R.C.S., L.R.C.P.

Roberts.—On Oct. 14, 1948, Philip Meredith Roberts, M.B., B.S., of Westcroft, Barton Court Avenue, Barton-on-Sea, Hants, aged 69.

Shanks.—While on holiday at Harrogate, William Shanks, M.B., Ch.B.Ed., of Sussex Road, Southport, aged 62.

Shennan.—On Oct. 21, 1948, at Fonthill Terrace, Aberdeen, Theodore Shennan, M.D.Ed. Hon.LL.D.Aberd., Professor of Pathology, Aberdeen University, 1914-36.

Shepard.—On Oct. 15, 1948, after an operation, Arthur Harold Shepard, M.D., of Spindleberry, Dogmersfield, Hants, formerly of Chelford.

Stephens.—On Oct. 8, 1948, at Hayne, Newquay, Cornwall, William John Stephens, M.R.C.S., L.R.C.P., aged 82.

Strang.—On Oct. 7, 1948, at Tighnamara, Belhaven, Dunbar, Thomas Morton Strang, M.B., Ch.B., D.P.H.

Symes.—On Oct. 11, 1948, at 37, Newstead Road, Southbourne, Bournemouth, William Legge Symes, M.R.C.S., aged 82.

Tozer.—On Oct. 10, 1948, Alfred Ernest Tozer, M.B., late Major, R.A.M.C., aged 67.

Wenyon.—On Oct. 24, 1948, Charles Morley Wenyon, C.M.G., C.B.E., M.B., B.S., F.R.S.

Winstanley.—On Oct. 12, 1948, at his home, Greenbank, Orrell, near Wigan, Henry Winstanley, L.R.C.P.&S.Ed., L.R.F.P.S.Glas., aged 83.

Young.—On Oct. 11, 1948, at Crowcombe House, Crowcombe, Taunton, Bertram Mitchell Young, M.R.C.S., L.R.C.P

Any Questions?

Correspondents should give their names and addresses (not for publication) and include all relevant details in their questions, which should be typed. We publish here a selection of those questions and answers which seem to be of general interest.

Para-aminosalicylic Acid

Q.—*In the Journal of July 17, 1948, p. 148, the treatment of pulmonary tuberculosis by para-aminosalicylic acid is discussed. Are there any contraindications to trying this drug on any case of tuberculosis? If so, what are they?*

A.—Lehmann introduced para-aminosalicylic acid as a result of experiments *in vitro* which suggested that it inhibited the growth of the tubercle bacilli by interfering with its metabolism. Favourable results have been reported by some authors in the treatment of exudative types of the disease and in tuberculous empyema. So far clinical trials have not been sufficiently extensive to prove the value of this drug, but the Medical Research Council is shortly to institute a controlled trial of its value. Until the results of this trial are known, indiscriminate use of the drug should be discouraged.

Chronic Tuberculous Cystitis

Q.—*What is the modern treatment of tuberculous cystitis? Should transplantation of the ureter into the rectum be considered in a patient who has had one kidney removed and in whom the cystitis remains obdurate?*

A.—The treatment of chronic tuberculous cystitis still remains a most difficult problem. Such a case as that mentioned should certainly have a course of tuberculin (T.R.). In some cases instillation of (*not* irrigations with) a 6% aqueous solution of carbolic acid will relieve symptoms, and, if cystoscopy should show these to be due to localized ulceration, much benefit often ensues from the use of high-frequency diathermy to the ulcer. In this case, as one kidney has already been removed and the infection still persists, grave suspicion attaches to the remaining kidney. Under these circumstances transplantation of the ureter would carry a high risk of superimposing secondary infection. In these cases, if transplantation is considered justifiable (and it often is), the skin is preferable to the bowel. Presumably it is frequency rather than pain that worries the patient. If pain were excessive pre-sacral neurectomy might be considered.

Preventing Abortion

Q.—*A patient who married at 39 became pregnant, but aborted at the fourth month. Now, five months later, she has again missed a period and is probably pregnant. Syphilis and uterine displacements have been ruled out, as have the usual other well-defined organic causes. It is important that she should have a living child. (a) Are there any measures which should be adopted by the patient in addition to the usual precautions such as rest and avoidance of alcohol, excessive sexual intercourse, strain, etc.? (b) Is treatment with progesterone justified, and if so in what doses and for how long? (c) Does vitamin E help to improve her chance of completing a successful pregnancy?*

A.—The occurrence of one abortion previously is not very significant, but in view of the circumstances of the case it is undoubtedly wise to take all reasonable precautions. It is not enough to ban excessive sexual intercourse: coitus should be avoided completely. Vitamin E can do no harm, although its value in these cases is disputed. If given, a large dose—20 mg. t.d.s.—of alpha-tocopherol is recommended. Thyroid, 1 gr. (65 mg.) daily, might also be given empirically. Progesterone therapy is probably best avoided unless there is some evidence of a deficiency of this hormone. Such evidence might be obtained by estimation of the output of pregnanediol. This test is carried out on a 24-hour or first morning specimen of urine (depending on the technique), but is undertaken by only a few laboratories in this country. If the pregnanediol excretion is low it would be wise to give 10 mg. progesterone intramuscularly two or three times weekly, starting immediately and continuing until the 28th or 32nd week of pregnancy. For further

details on pregnanediol tests and progesterone therapy in threatened and habitual abortion reference should be made to an article by S. Bender which appeared recently in the *British Medical Journal* (1948, **1**, 683) and to an annotation in the same issue (p. 696).

Inheritance of Deformities

Q.—*Is termination of pregnancy justified in a case where the only child, now 11 years old, has gross congenital deformities? In the case I have in mind the mother was normal until four weeks from term, when she developed generalized oedema. At birth there was a breech presentation with extended arms and legs; both fibulae were absent and there was valgus deformity of the feet. What is the likelihood of the mother giving birth again to a child with congenital abnormalities?*

A.—This type of congenital deformity seems to occur sporadically, at least in the great majority of instances, and there seems to be little evidence that heredity is a factor of importance. It is true that there appears to be a general tendency for a woman who has had a deformed child to have a somewhat increased chance of bearing another—not always with the same type of deformity. The increased risk is a small one, however, and the chance that the present pregnancy will result in a deformed child is probably not much greater than the 1 in 40 or so for any random pregnancy. The mother can be reassured that the odds are heavily on the side of the child, and in the writer's opinion abortion could not be justified on genetic grounds.

Use of Detergent Solutions

Q.—*What is the usual composition of proprietary liquid detergents? Can you tell me if there is any danger in or contraindication to their use for the following purposes: (a) washing of dishes and other domestic utensils, and (b) personal ablution?*

A.—It is not possible to discover the composition of a detergent which is a proprietary preparation. Many detergents, however, have similar properties, and it is a general rule that there is little danger from their use in washing dishes and utensils. For personal ablutions, however, they may give rise to dermatitis in sensitive subjects. Very severe dermatitis has followed the use of detergents as hair shampoos.

Paronychia

Q.—*Can you suggest any effective treatment for a woman, aged 42, with a chronic paronychia of 7½ months' duration? There is a slight discharge of pus containing staphylococci every month or so, and a kaolin poultice gives relief on these occasions, which are of short duration. In the intervals the skin around the nail-fold remains swollen and the nail has become wrinkled. Operation is not indicated.*

A.—If ringworm and monilia infection have been excluded as causes of the paronychia, treatment should aim at keeping the part dry, using radiant heat or short-wave diathermy locally or fractional doses of *x* rays and the following paint:

R	Mercury perchloride	1%
	Brilliant green	1%
	Spirit	ad 100%

Make a paint.

An impaired peripheral circulation may play a part in the aetiology, in which case small doses of phenobarbitone and thyroid are helpful.

Adolescent Obesity

Q.—*A girl of 18 has put on 1½ st. (9.5 kg.) in weight during the past twelve months. One sister (three years older) was obese when much younger; there is no other family tendency to obesity. There is little evidence of over-eating, except perhaps that she is a little too fond of sweets. Do girls in the late teens often tend to put on weight for a year or two? What investigations are necessary, and what is the most likely cause?*

A.—It is more usual for the weight to be put on in the early teens—that is, at and after puberty—and for some of this to be lost in the later teens. The writer, who believes that adiposity is due to hyperactivity of the pituitary and adrenal glands rather than to any endocrine deficiency, considers that this increase in weight is associated with greater activity of the pituitary gland at this phase in people of certain endocrine constitution. In the absence of other endocrine stigmata it is unlikely that investigations would reveal any gross lesion in this patient. Apart from an endocrine constitution as indicated above, one can only speculate on other causes, and that to no great purpose.

Hot Flushes

Q.—*Is there any treatment for repeated hot flushes and sweats? A woman aged 53, who has had four children, was well until 1943, when her uterus was removed for fibroids. In 1944 she had acute rheumatism, which left her with mitral stenosis. Her blood pressure has gradually increased, until now it is about 200/105 mm. The hot flushes and sweats average about thirty a day and leave her exhausted. No treatment has had any effect.*

A.—It would be helpful to know what treatment has been tried. If the flushes and sweats are menopausal, as seems likely, they should respond to oestrogens. If they do not, then either the diagnosis is incorrect or previous oestrogen therapy may have been badly planned so that the patient has become resistant to it. Unless previously tried without effect, oestrogen should be given according to the usual technique, starting with the smallest possible dose which is sufficient to control rather than eliminate the flushes, and then gradually reducing this dose over the course of two or three months. Alternatively, empirical treatment with α-tocopherol, 60 to 100 mg. daily, or large doses of calcium, or small doses of thyroid, might be tried. The usual remedies for hypertension—rest and phenobarbitone, etc.—should be applied simultaneously. Symptoms of the kind described sometimes have a psychological basis.

NOTES AND COMMENTS

Unauthorized Quotation.—The solicitors to the Medical Defence Union have asked us to publish the following letter from Messrs. H. B. Wedlake Saint and Co.: "On behalf of our clients, Silten Limited, of Silten House, Hatfield, Herts, we refer to your letter of Sept. 24. Our clients have noted that you have been consulted by Professor L. S. P. Davidson and Dr. J. J. R. Duthie with regard to the use by our clients of your clients' names and the quotation from the section of the book on the treatment of rheumatic diseases, written by your clients, in connexion with our clients' preparation 'Leucotropin.' Our clients appreciate that it is considered grossly improper for a member of the medical profession to be associated with the sale of a proprietary remedy, and express their sincere regret that the pamphlet circulated by them gives the impression that your clients were advocating the use of our clients' preparation and are the authors of our clients' pamphlet. Our clients admit that the use of the names of your clients was unauthorized and fully apologize for the improper use of their names and the unauthorized quotation from the book written by your clients. Our clients undertake to withdraw the pamphlet from circulation forthwith and to destroy all pamphlets in their possession and to pay the costs incurred by your clients. Our clients have noted that your clients reserve to themselves the full right to publish this apology in the medical press or in such other manner as may be necessary to undo the harm which is likely to result to them from the improper use of their names."

Guide to the B.P.—British Drug Houses, Ltd., has recently published a new edition of its *B.D.H. Guide to the B.P., 1948*. It is available free to members of the medical profession. The purpose of the *Guide* is "to direct the attention of physicians and pharmacists to the alterations which have been made in the new Pharmacopoeia," with particular reference to the articles and preparations which are different from the corresponding ones in the 1932 *B.P.* and to those which have become official for the first time.

Correction.—In the letter from Dr. M. J. Fenton in the *Journal* of Oct. 16 (p. 723) there was a misprint in the name of the substance used for the treatment of burns—the correct name of the substance is silver dinaphthylmethane disulphonate.

All communications with regard to editorial business should be addressed to THE EDITOR, BRITISH MEDICAL JOURNAL, B.M.A. HOUSE, TAVISTOCK SQUARE, LONDON, W.C.1. TELEPHONE: EUSTON 2111. TELEGRAMS: *Aitiology, Westcent, London.* ORIGINAL ARTICLES AND LETTERS forwarded for publication are understood to be offered to the *British Medical Journal* alone. Authors desiring REPRINTS should communicate with the Publishing Manager, B.M.A. House, Tavistock Square, W.C.1, on receipt of proofs.
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